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GENOME-WIDE SPERM DNA METHYLATION CHANGES AFTER THREE MONTHS OF EXERCISE TRAINING IN HUMANS

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Abstract

Aim: DNA methylation programs gene expression and is involved in numerous biological processes. Accumulating evidence supports transgenerational inheritance of DNA methylation changes in mammals via germ cells. Our aim was to determine the effect of exercise on sperm DNA methylation.

Materials and Methods: Twenty-four men were recruited and assigned to an exercise intervention or control group. Clinical parameters were measured and sperm samples were donated by subjects before and after the three month time-period. Mature sperm global and genome-wide DNA methylation was assessed using an ELISA assay and the 450K BeadChip (Illumina).

Results: Global and genome-wide sperm DNA methylation was altered after three months of exercise training. DNA methylation changes occurred in genes related to numerous diseases such as Schizophrenia and Parkinson's disease.

Conclusions: Our study provides the first evidence showing exercise training reprograms the sperm methylome. Whether these DNA methylation changes are inherited to future generations warrants attention.

Executive summary

Aim

- To determine the impact of exercise training on human sperm DNA methylation.

Materials and Methods

- Twenty-four healthy young men were recruited and allocated to an exercise training or control group.
- Health and fitness parameters were measured and sperm samples were collected before and after three months.
- Global and genome-wide DNA methylation was quantified using an ELISA assay and the Infinium HumanMethylation450 BeadChip (Illumina), respectively.
- Significant alterations in CpG methylation and corresponding gene pathways modulated by exercise training were analysed using Partek (Genomic Suite). The disease association was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID).

Discussion

- Exercise training was associated with global demethylation of human sperm.
- DNA methylation changes occurred across the genome after exercise training in genes enriched for numerous developmental processes and pathways associated with the adaptation to exercise training.
- Genes related to disease were methylated after exercise, indicating transcriptional silencing.

Conclusions

- We provide the first evidence demonstrating exercise training regulates the human sperm methylome at CpG sites in genes associated with disease.

Introduction

DNA methylation is crucial for long-term gene expression regulation [1, 2]. DNA methylation is, however, reprogrammable through environmental conditions [3, 4]. Aberrant DNA methylation signatures are associated with age-related diseases such as cancer [5-7], atherosclerosis [8, 9], type 2 diabetes mellitus [10, 11], Alzheimer's disease [12] and major psychosis disorders [13, 14].

Mounting evidence indicates that environmentally induced DNA methylation changes are inherited by subsequent generations and affects their phenotypes [15-22]. A likely mechanism for inheritance of DNA methylation profile is via the germ cells. Interestingly, aging is associated with sperm DNA methylation changes and may influence disease risk of future generations [23, 24]. The differentially methylated regions in sperm obtained from old (12–14 month-old) versus young (3-month-old) mice were observed in the brain of the subsequent offspring, causing altered gene expression and increased behaviors associated with psychiatric disorders (schizophrenia and autism spectrum disorder) [24]. Although aging has been investigated in context with sperm DNA methylation, the influence of other favorable environmental stimuli are yet to be determined.

We recently found that exercise training significantly improves cardiorespiratory fitness and lipid profile in conjunction with genome-wide leukocyte methylation changes in young men [25]. Others have shown that exercise training modulates skeletal myocyte [26-28] and adipocyte [29] DNA methylation as well as improving

health and fitness phenotypes. Thus, somatic cells are vulnerable to epigenetic changes caused by exercise training, but whether exercise training regulates DNA methylation is germ cells (oocyte or sperm) is currently unknown.

The aim of this study was to determine the impact of exercise training on human sperm DNA methylation. Considering the mounting evidence supporting exercise training as an environmental modulator of somatic cell DNA methylation [25-29], we hypothesized that exercise training would significantly modify sperm DNA methylation in genes related to human diseases.

Materials and methods

Subjects

Twenty-four healthy young men were recruited for this study. Subjects were non-smoking, not taking any medications and free from any age-related chronic diseases, according to self-administered health questionnaires. Subjects were eligible if they had not engaged in any structured high-intensity aerobic exercise training during the past six months and were recruited predominantly from the University by flyers and by word-of-mouth.

The subjects' characteristics are outlined in Table 1. All subjects gave written informed consent to participate and this study was approved by the Federation University Australia Human Research Ethics Committee.

Procedures

On the initial day of testing, subjects were asked to complete health and physical activity questionnaires in order to establish their eligibility to participate in the study. Subjects were also familiarized with the testing procedures to follow and were given a collection tube for their sperm donation.

The second testing session involved a sperm donation, blood donation, physical measures and a test of maximal oxygen uptake ($\dot{V}O_{2max}$) on a treadmill. All testing sessions were performed in the morning (7–10 AM). Height, weight and body mass index were recorded using scales and a stadiometer. Blood pressure was measured and augmentation index was assessed by non-invasive applanation tonometry using the SphygmoCor instrument (AtCor, Australia). Subjects completed a maximal treadmill exercise test to assess $\dot{V}O_{2max}$. After a three minute warm-up, subjects began running at 10 $km \cdot h^{-1}$ and the treadmill speed was progressively increased by 1 $km \cdot h^{-1}$ every second minute until the volitional exhaustion or the supervising Exercise Physiologist deemed it appropriate to stop the test. Participants were fitted with a two-way breathing valve (Hans Rudolph) and breath-by-breath analysis was performed by the online metabolic system (Moxus, Modular, USA). $\dot{V}O_{2max}$ was determined as the highest O_2 value averaged over 60 s. Maximal treadmill speed was deemed the highest speed successfully completed and was adjusted for time so that participants were encouraged to exercise to their limit. The same testing procedures were completed 3–5 days after the cases' final exercise session or three months after their initial donation for controls.

Sperm and blood processing

Subjects gave resting preprandial sperm and blood donations before and after the three month exercise intervention. Following an overnight fast, subjects extracted their sperm by masturbating at home and donated their sample to the researchers at the University within 30 min of extraction. All sperm donations and analyses were performed according the World Health Organization's recommendations. Sperm cell number and vitality was assessed by the same researcher using a sheep-counter. Mature, motile sperm were isolated from lymphocytes, epithelial cells, immature or

abnormal sperm and other cellular debris using the PureSperm 40/80 reagents (Nidacon). Briefly, 2 ml of PureSperm 40 was carefully layered on top of PureSperm 80, followed by gently aliquoting 1.5 ml of ejaculate onto the density gradient. The density gradient was spun at 300 G for 20 min. The mature sperm were pelleted and supernatant was removed. The pellet was washed twice by resuspending it in 5 ml of PBS before being spun at 500 G for 10 min. DNA was extracted from mature sperm suspended in 200 µl of PBS using the Purelink Genomic DNA Mini kit (LifeTechnologies) following the manufacturer's recommendations with some small adjustments. To deform the tightly packaged DNA in mature sperm, 0.03 mmol of DL-Dithiothreitol solution (Sigma-Aldrich) was added to the sample before the addition of proteinase K solution and the protein digestion step (incubation at 55°C) was extended from the recommended 10 min to 90 min. All extractions were performed immediately after sperm donation to prevent any temporal *de novo* influences on DNA methylation. DNA yield was assessed using the Nanodrop 2000 Spectrophotometer (Thermo Scientific) before being stored at -20°C.

A preprandial blood sample (24 ml) was drawn from the antecubital vein into serum separating tubes with the subject seated, using standard phlebotomy procedures. Blood was immediately stored on ice before further processing. Blood lipid assays were performed as described previously [25].

Global DNA methylation analysis

Average global DNA methylation of sperm from all subjects was quantified using the 5-mC ELISA Kit (Zymo Research, USA). All experiments were performed according to the manufacturer's procedures. All paired samples before and after the intervention were run on the same plate, as well as 100% methylated and 0% methylated controls, all run in duplicate with a standard curve. Absorbance was

measured at 450 nm using the Multiskan FC Microplate Photometer (Thermo Scientific, Australia) and average DNA methylation was calculated using the formula generated from the standard curve. The average intra-assay coefficient of variation for duplicate samples was 4.85%.

Genome-wide DNA methylation analysis

Genome-wide sperm DNA methylation was quantified in 12 cases before and after the exercise intervention using the Infinium HumanMethylation 450K BeadChip (Illumina) as previously described [25]. Experiments were conducted following the manufacturer's guidelines, with the help of the Busselton Population Medical Research Institute. Briefly, raw *β*-values underwent Subset-quantile Within Array Normalization (SWAN) and were transformed to M-values using the logit function ($\log^2$ (β/(1- β))) before analyzing differentially methylated CpG sites after exercise training. M-values were converted to *β*-values for representation of differentially methylated CpG sites in tables and graphs because they correspond to the percentage of CpG methylation and are a good biologically relevant representation. Genome-wide DNA methylation data was analyzed using Partek (Genomic Suite, version 6.6).

Exercise training

Subjects were randomly allocated to either an exercise training (cases) or control group. Cases completed sprint interval training twice weekly for three months. Three months of exercise training was chosen because it covered one human spermatogenesis cycle. The controls did not engage in any form of training but were asked not to deviate from their routine physical activity habits. All subjects were asked to adhere to their normal diet. The sprint interval training schedule is outlined

in Table 2. Sprint interval training is an effective type of exercise training that rapidly improves cardiorespiratory fitness and endurance performance [30-33].

The exercise training protocol of this study was based on research shown to improve cardiorespiratory fitness and endurance performance [25, 34], but with some adjustments, to avoid overuse injuries that could occur with an extended training period (three months). Subjects completed 30 s sprints at maximal intensity with a passive four minute rest period between efforts. Training began with three sprints and was progressed by one effort every fortnight until week 7, when sprints were kept at six efforts for the remaining six weeks of the intervention. Before each session, subjects completed a short warm-up entailing a light 5 min jog, dynamic stretches and some 20 m sprints at 70, 80, 90 and 100% of maximal effort. Training was performed on the University's athletics oval and subjects were supervised and given constant encouragement during sprints by an Exercise Physiologist.

Statistical analyses

Kolmogorov-Smirnov and Shapiro-Wilks were performed to assess normality. Two-tailed paired *t*-tests were used to assess within-subject changes to physical, health and fitness variables. A repeated measures ANOVA was used to determine the interaction between global sperm DNA methylation before and after the intervention in relation to cases and controls using IBM SPSS for Windows (version 21). Differentially methylated CpG sites in cases were determined by repeated measures ANOVA using Partek (Genomic Suite, version 6.6). In order to control for false positives, a false discovery rate correction (FDR, $q \leq 0.1$) was applied to genome-wide data by converting *p*-values to *q*-values. Hierarchical clustering, gene ontology and pathway analysis on genome-wide CpG methylation data were performed using Partek (Genomic Suite, version 6.6). Disease annotation analysis was conducted

using the Database for Annotation, Visualization and Integrated Discovery (DAVID, version 6.7). Statistical significance was set at $p<0.05$.

Results

Exercise training improved cardiorespiratory fitness

To determine whether exercise training alters human sperm DNA methylation, 13 untrained male volunteers completed three months of exercise training using a modified training protocol (Table 2) previously shown to improve cardiorespiratory fitness and induce genome-wide DNA methylation changes in leukocytes [25]. Although $\dot{V}O_{2max}$ was unchanged (2.2%, $p=0.35$), relative to baseline, the cases, on average, had a significantly lower resting heart rate by 10 beats·min^{-1} and completed an extra one min at a significantly higher maximal treadmill speed ($p=0.01$ and $p=0.002$, respectively), while controls showed no significant changes in these variables (Table 1).

To assess whether exercise training influences average sperm DNA methylation, we assessed global sperm DNA methylation in cases and controls using ELISA-based chemistry. After adjusting for ELISA plate, relative to the unchanged global sperm DNA methylation observed in controls (n=11, 4.09%), sperm DNA was significantly de-methylated after three months of exercise training (n=13, -6.63%, interaction $p=0.006$) (Figure 1A and B).

Based on the global DNA methylation results we only quantified genome-wide sperm DNA methylation in 12 cases before and after three months of exercise training using the 450K BeadChip (Illumina). After applying a FDR ($q\leq0.1$), we found DNA methylation changes occurred throughout the genome in relation to the nearest gene and CpG islands (Figure 1C and D). Of these, 7509 CpG sites relating to 4602

genes had significant DNA methylation changes ranging from 0.3 to 6.2% after exercise training (Figure 1E and 2). More CpG sites were demethylated rather than methylated after exercise training (4275 vs 3233, respectively). The top 25 methylated and demethylated CpG sites after exercise training are outlined in Table 3.

To gain insight into the biological impact of the CpG methylation changes following exercise, we performed gene ontology and pathway analysis. Genes with altered CpG methylation were those enriched for crucial biological processes including developmental process, anatomical structure, embryonic morphogenesis and organ development (Figure 3 and Supplementary Table 1). Pathway analysis revealed genes with CpG site DNA methylation changes were enriched for pathways such as MAPK signaling, PI3K-Akt signaling, pathways in cancer and ErbB signaling (Table 4).

In the search for the most biologically relevant CpG methylation changes, we focused on CpG sites with a ≥1.5% increase (n=703) or decrease (n=1247) in methylation after exercise training and entered them into DAVID for disease annotation analysis. While genes with demethylated CpG sites were those relating to normal variation, those with increased methylation were enriched for numerous diseases, with the most overrepresented diseases being Schizophrenia, Parkinson's Disease, autism, cervical cancer and leukemia (Figure 4).

The global erasure of sperm CpG methylation that occurs after fertilization is well established [35-37]. The sperm CpG methylation at imprinted genes, however, are resistant to the global erasure after fertilization [38, 39] and as such, these genes are key candidates for possible transgenerational inheritance through sperm. We found 16 paternally imprinted genes were differentially methylated after the three month

exercise training intervention (Table 5), in genes associated with pathologies including EKG abnormalities (*KCNQ1OT1* and *KCNQ1*), autism and alcohol dependence (*GABRG3*), Tourette syndrome, obsessive compulsive disorder and dystonia (*SGCE*), and Alzheimer's disease, obesity, type 2 diabetes mellitus, blood pressure and atherosclerosis (*IGF2* and *INS-IGF2*).

Discussion

Unlike the genome, the epigenome is malleable to changing environments and these changes are somewhat heritable [3, 4]. Germ cells (sperm and oocytes) are likely vectors that transfer environmentally-affected DNA methylation profiles to future generations. We are the first to show the exercise training-induced DNA methylation changes in human sperm. We found exercise training significantly manipulated genome-wide DNA methylation and most strikingly, increased methylation in disease-associated genes indicating transcriptional silencing. Moreover, methylation changes occurred in paternally imprinted genes that are exempt from the DNA methylation erasure after fertilization [38, 39].

Mounting evidence has demonstrated the capacity of exercise training to influence the human DNA methylome in numerous tissues, including skeletal myocytes [26-28], adipocytes [29] and leukocytes [25]. Exercise training or increased physical activity tends to be associated with a reduced level of somatic cell global DNA methylation. Leukocyte DNA methylation was anti-correlated to levels of physical activity in 509 older adults (>70 y) [40] and we previously reported more demethylated leukocyte CpG sites in response to a four week exercise training intervention in young men [25]. Furthermore, global and gene-specific demethylation occurred after acute exercise in human skeletal myocytes [41]. In the present study,

we found global sperm DNA methylation was reduced after three months of exercise training, suggesting that exercise may systemically demethylate both somatic and germ cells. Interestingly, older adults have more heavily methylated global sperm DNA compared to their younger counterparts [23, 42]. Also defective human sperm exhibit nearly two-fold higher levels of global DNA methylation [43]. To that end, the global demethylation observed in our subjects after exercise training could be favorable, possibly counteracting the increased DNA methylation associated with ageing. This, in turn, could positively influence fertility though future studies are necessary.

Interestingly, exercise training was associated with sperm methylation changes to CpG sites in genes related to pathways and biological processes similar to those observed in skeletal muscle [26] and leukocytes [25] from previous studies. For example, pathways regulated by exercise training-induced leukocyte DNA methylation alterations [25] that were also observed in sperm include MAPK signaling, PI3K-Akt signaling and pathways in cancer. Similarly, overlapping pathways between skeletal muscle [26] and sperm pathways modulated by exercise training include MAPK signaling, insulin signaling and ErbB signaling. Therefore, it would seem that some exercise-responsive genes (CpG sites) are regulated by DNA methylation in human somatic cells and also in sperm.

The genes with CpG methylation changes in the present study were enriched for numerous molecular and cellular processes including anatomical structure development and morphogenesis, single-organism development and embryonic morphogenesis. Genes with exercise-induced CpG methylation changes were also associated with many debilitating diseases such as Schizophrenia, Parkinson's disease, cervical cancer, leukemia and autism. The genes associated with diseases

were methylated after exercise training, indicating that these genes may have been transcriptionally silenced. Age-associated sperm CpG methylation patterns were observed in genes implicated in Schizophrenia in humans [23] and mice [24]. Some of the adverse DNA methylation patterns found in sperm of aged mice was transmitted to the brain of their offspring, leading to transcriptional dysregulation of genes involved in schizophrenia and autism, facilitating the disease-related traits [24]. Furthermore, offspring (F1 to F3) of gestating female rats treated with endocrine disruptors (bisphenol-A, bis[2-ethlhexyl]phthalate and dibutyl phthalate and vinclozolin) have altered sperm DNA methylation and an increased risk of testis disease, obesity and infertility [15, 44, 45]. These environmentally-induced DNA methylation aberrations led to transcriptional changes in common pathways across numerous somatic cells, including those regulated in the present study (MAPK signaling, insulin signaling and pathways in cancer) [46]. Whether the altered sperm DNA methylation observed in our subjects will be transmitted to their offspring and prevent the development of disease is speculative and would require large human studies involving the analysis of multiple generations.

Germ cells undergo global demethylation following fertilization [35, 39]. Consequently, the likelihood of such CpG methylation changes surviving this demethylation event is uncertain. We did, however, reveal a number of paternally imprinted genes (e.g. *IGF2*, *INS-IGF2*, *SGCE* and *GABRG3*) had differentially methylated CpGs after exercise training. These genes are exempt from the global demethylation after fertilization [38, 39] and as such, are key candidates for exercise-induced transgenerational inheritance of DNA methylation gene programming. Our disease analysis using DAVID revealed the differentially methylated paternally imprinted genes after exercise training were related to neurological disorders

(autism, Alzheimer's disease, Tourette's syndrome and obsessive compulsive disorder) and cardio-metabolic diseases (obesity, type 2 diabetes mellitus, high blood pressure and atherosclerosis). Whilst no evidence exists, it is tempting to speculate that exercise training may remodel the sperm methylome and that this epigenetic modification may reduce the disease risk of offspring.

DNA methyltransferase enzymes (DNMT1, DNMT3A, DNMT3B and DNMT3L) as well as ten-eleven translocation (TET1, TET2 and TET3) proteins could be modulated by exercise training leading to altered DNA methylation. Our study was not designed to target the exact physiological or molecular mechanism by which exercise training influences DNA methylation in sperm, rather it was designed to investigate whether exercise training influences sperm DNA methylation. Therefore, further research is required to identify the molecular mechanisms evoking the changes in the sperm methylome after exercise training.

Our study has several limitations. Firstly, our study had a modest sample size and there was a statistically different global sperm DNA methylation between cases and controls at baseline. While we acknowledge this is not desirable, our statistical analysis accounted for the observed difference. We do, however, recommend that our results should be verified in a larger population. The relative exercise workload was not standardized. We did, however, ask that all subjects perform each sprint maximally without pacing to ensure they are working at maximal intensity. Certain diets are associated with DNA methylation levels in somatic cells [47, 48]. Despite asking our subjects not to deviate from their routine dietary habits, the lack of control for diet in our study should also be acknowledged. Finally, we did not control for genotype-DNA methylation interactions or quantify DNA methylation in context with other epigenetic modifications or gene expression. Nonetheless, our novel finding

that exercise alters human sperm DNA methylation should encourage future investigations into the influence of exercise training on germ cell epigenetic modifications and gene regulation.

Conclusions

We report for the first time that exercise training significantly modifies the human sperm methylome. Whilst exercise training was associated with an increased global sperm demethylation overall, methylation in key genes associated with human disease was increased indicating transcriptional silencing of these genes.

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Competing interests

The authors have no competing interests to disclose.

Figure Legends

Figure 1. Sperm DNA methylation changes after exercise training. Average percent (±SE) of global sperm DNA methylation is given for 13 cases (A) and 11 controls (B) after the three month intervention. Relative to the controls who showed no global methylation change, cases exhibited a global demethylation (-6.63%) after three months of exercise training (mean±SE: 39.1±3.85 to 43.2±3.6 and 52.95±3.56 to 46.3±3.4, respectively, interaction p=0.006). Data are from repeated measures ANOVA adjusting for ELISA plate number. Genome-wide DNA methylation changes at CpG sites in relation to the nearest gene (C) and CpG islands (D) are shown**.** Data are from Chi^2 tests. E) The number of CpG sites with increased methylation (black bars) and decreased methylation (grey bars) are given on the y-axis with the

magnitude of change illustrated on the x-axis. Data are from differentially methylated CpG sites ($q \leq 0.1$).

Figure 2. Hierarchical clustering of CpG sites after three months of exercise training. The CpG methylation status is indicated by blue (low methylation) and yellow (high methylation) from 12 subjects before (grey bar) and after (purple bar) three months of exercise training. Each branch of the array tree on the left of the purple and grey bars are subjects. The array tree at the top of the hierarchical cluster indicates clusters of CpG sites modified by exercise training. Data are from differentially methylated CpG sites ($q \leq 0.1$).

Figure 3. Gene ontology for genes with differentially methylated CpG sites after exercise training. Genes with altered CpG site methylation after exercise are grouped for function on the y-axis with corresponding enrichment scores on the x-axis. Data are from differentially methylated CpG sites ($q \leq 0.1$).

Figure 4. Disease annotation analysis for genes with differentially methylated CpG sites after exercise training. Data are from genes with a ≥1.5% increase or decrease in methylation after exercise training ($q \leq 0.1$). The y-axis represents the number of genes for each annotated disease (x-axis).

Table 1. Participant characteristics before and after three months of exercise training.

Variable	Cases (n=13)		Controls (n=11)	
	Before Exercise	After Exercise	Before	After
Age (y)	24.4±5.19		22.45±4.74	
Ht (cm)	181.1±6.54		177.95±4.07	
Wt (kg)	83.58±10.7	84.01±11.97	82.22±11.83	82.93±10.64
BMI (Wt/Ht^2)	25.53±3.34	25.89±3.61	25.94±3.5	25.9±3.08
HR ($beats \cdot min^{-1}$)	**78.54±15.64**	**68.23±7.15***	68.18±11.58	66.45±8.19
SBP (mm Hg)	130.46±11.82	129.85±10.64	123.45±9.2	123.09±10.24
DBP (mm Hg)	77.23±9.87	76.38±7.85	75.82±8.51	72.27±7.14
CSBP (mm Hg)	110.92±9.86	111.08±8.43	106.91±8.38	105.72±9.32
CDBP (mm Hg)	76.08±17.35	77.69±7.77	76.36±8.64	73.64±7.38
Aix (%)	-4.15±9.73	-4.15±8.73	-2.36±12.8	-1.18±11.71
Cholesterol (mmol/l)^	4.82±0.88	4.77±1.04	4.01±1.0	3.97±0.77
Triglyceride (mmol/l)^	1.01±0.48	1.07±0.46	0.9±0.38	0.82±0.18
HDLC (mmol/l)^	1.43±0.25	1.43±0.3	1.37±0.2	1.29±0.14
LDLC (mmol/l)^	2.92±0.79	2.87±0.88	2.22±0.75	2.32±0.74
Glucose (mmol/l)^	4.78±0.38	5.22±0.52	4.9±0.46	4.92±0.31
Insulin (mmol/l)^	6.94±2.72	10.72±6.44	7.15±3.65	12.78±16.42
$\dot{V}O_{2max}$ ($ml \cdot kg \cdot min^{-1}$)	47.43±5.64	48.47±6.0	45.85±7.34	44.92±5.49
Maximal treadmill speed ($km \cdot h^{-1}$)	**14.4±1.12**	**14.9±1.11****	14.07±1.52	13.84±1.8
Sperm volume (ml)	4.7±1.4	5.17±0.87	3.95±1.7	3.97±1.79

Sperm #	$1.35\times10^{9}\pm 1.21\times10^{9}$	$1.39\times10^{9}\pm 1.41\times10^{9}$	$1.58\times10^{9}\pm 1.56\times10^{9}$	$1.33\times10^{9}\pm 1.39\times10^{9}$
Sperm alive (n)	$9.12\times10^{8}\pm 1.09\times10^{9}$	$9.08\times10^{8}\pm 1.02\times10^{9}$	$8.36\times10^{8}\pm 1.07\times10^{9}$	$6.05\times10^{8}\pm 4.68\times10^{8}$
Sperm alive (%)	61.65±24.42	62.72±13.77	48.26±23.26	53.89±14.14

Legend: Ht, height; Wt, weight; BMI, body mass index; HR, resting heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CSBP, central (aortic) blood pressure; CDBP, central (aortic) diastolic blood pressure; augmentation index; HDLC, high-density lipo-protein cholesterol; LDLC, low-density lipoprotein cholesterol; $\dot{V}O_{2max}$, maximal oxygen uptake; ^, n=8; #, number; %, percentage. Data are from two-tailed paired t-test and expressed as mean±SD. Sperm analysis was conducted on semen samples and not from highly motile sperm isolated using the PureSperm 40/80 reagents (Nidacon).

592 Table 2. Description of the three month exercise program.

Week	Session #	Training load*	Training sprint time (min)	Total session time (min)
1	1	3 sprints	1.5	9.5
	2	3 sprints	1.5	9.5
2	3	3 sprints	1.5	9.5
	4	3 sprints	1.5	9.5
3	5	4 sprints	2	14
	6	4 sprints	2	14
4	7	4 sprints	2	14
	8	4 sprints	2	14
5	9	5 sprints	2.5	18.5
	10	5 sprints	2.5	18.5
6	11	5 sprints	2.5	18.5
	12	5 sprints	2.5	18.5
7	13	6 sprints	3	23
	14	6 sprints	3	23
8	15	6 sprints	3	23
	16	6 sprints	3	23
9	17	6 sprints	3	23
	18	6 sprints	3	23
10	19	6 sprints	3	23
	20	6 sprints	3	23
11	21	6 sprints	3	23
	22	6 sprints	3	23
12	23	6 sprints	3	23
	24	6 sprints	3	23

Total Time	120	60	454

Legend: # number; * all sprints were completed at maximum intensity, separated by a four minute passive recovery.

595 Table 3. DNA methylation changes after three months of exercise training ($q \leq 0.1$).

Location in relation to					***DNA methylation (%)***				
CpG site	**Closest gene**	**Gene region**	**CpG island**	**Chr**	**Before (mean±SD)**	**After exercise (mean±SD)**	**Δ**	***p*-value**	***q*-value (≤0.1)**
cg02598618	-	-	Open sea	10	94.0±1.4	98.6±1.1	4.6	1.79×10^{-5}	0.06
cg02655397	-	-	N shelf	11	80.7±4.4	85.1±3.3	4.5	0.0005	0.08
cg10243075	*CACNA1A*	Body	N shore	19	23.2±3.6	27.6±5.0	4.4	0.0004	0.08
cg27222157	*RBM14*	TSS1500	N shore	11	22.2±6.8	26.5±8.5	4.4	0.0009	0.08
cg10413297	*RFPL3S*	TSS1500	Open sea	22	25.6±6.7	29.7±6.6	4.1	0.001	0.09
cg16533336	*WBSCR17*	Body	Open sea	7	76.7±2.6	80.8±2.3	4.1	1.17×10^{-7}	0.02
cg09194930	*MT1L*	TSS200	Island	16	14.7±9.5	18.8±12.7	4.1	0.001	0.09

cg00685853	-	-	N shore	2	14.4±3.9	18.4±6.2	4.0	0.0001	0.07
cg27205941	*GMDS*	TSS200	Island	6	29.0±4.1	32.9±3.5	4.0	0.001	0.09
cg17745251	*C10orf140*	Body	Island	10	25.0±2.7	29.0±3.0	4.0	0.002	0.09
cg25485435	*RAMP1*	TSS1500	N shore	2	16.9±3.5	20.8±3.0	3.9	0.0002	0.07
cg11888420	-	-	Open sea	6	33.0±2.7	36.8±4.6	3.8	0.001	0.09
cg08715827	-	-	Open sea	12	6.1±2.3	9.8±5.8	3.8	0.001	0.09
cg15617548	*GORASP2*	5'UTR 1stExon	Island	2	23.5±2.8	27.1±2.8	3.7	0.0009	0.08
cg15488194	*MBNL1*	TSS1500 5'UTR	Open sea	3	23.9±11.9	27.5±12.8	3.7	0.002	0.097
cg17271592	*HIST2H2AA4* *HIST2H2AA3*	TSS1500	Island	1	13.8±3.1	17.4±2.6	3.6	0.0006	0.08
cg06785129	*RFPL3*	TSS1500	Open sea	22	18.6±3.2	22.2±4.2	3.6	0.002	0.09

cg14047339	*RUNX2*	Body	Island	6	33.7±2.2	37.3±2.9	3.6	0.002	0.09
		5'UTR							
	SUPT3H	1stExon							
		5'UTR							
cg13916261	*FNBP1*	Body	N shelf	9	24.4±3.9	27.9±4.9	3.5	0.0003	0.08
cg09303484	-	-	Open sea	7	63.3±4.3	66.8±3.6	3.5	0.0008	0.08
cg05528975	-	-	Open sea	2	25.9±2.5	29.4±3.1	3.5	0.0005	0.08
cg17627829	*HCG18*	Body	N shore	6	9.5±3.4	13.0±4.1	3.5	0.002	0.09
cg05629323	*TFDP3*	3'UTR	Open sea	X	8.8±2.7	12.3±4.4	3.5	0.002	0.09
		1stExon							
cg20681184	*PIK3CD*	5'UTR	S shore	1	14.5±2.8	18.0±4.5	3.5	0.002	0.09
cg15069995	*HORMAD1*	5'UTR	Open sea	1	5.9±2.1	9.3±3.9	3.4	0.0009	0.08
cg13062455	*SEL1L*	Body	Open	14	88.2±2.3	85.4±3.3	-2.9	1.27×10^{-5}	0.05

			sea						
cg24360197	-	-	Open sea	15	70.1±8.4	67.2±7.9	-2.9	0.001	0.09
cg03359503	*CLIC2*	5'UTR 1st Exon	Open sea	X	87.7±4.1	84.7±.5	-3.0	0.0009	0.08
cg24121979	-	-	Open sea	12	94.9±3.2	91.9±2.0	-3.0	0.0003	0.08
cg20909579	*PDE6B*	TSS1500 Body	Island	4	89.6±2.9	86.6±5.4	-3.0	0.0008	0.08
cg02507663	*NCRNA00219 SNORA13*	Body TSS200	S shore	5	54.9±8.4	51.9±8.4	-3.0	0.001	0.09
cg27569203	*CELSR1*	Body	Island	22	90.2±2.4	87.3±1.6	-3.0	0.002	0.09
cg26235273	*DKK3*	3'UTR	Open sea	11	71.0±4.0	67.8±3.8	-3.1	0.0006	0.08
cg17518550	*C1orf150*	TSS200	Open sea	1	82.3±4.0	79.2±6.4	-3.1	0.001	0.09

cg16514287	*SLC25A36*	Body	Open sea	3	94.0±1.4	90.8±1.1	-3.1	1.7×10^{-6}	0.03
cg26057840†	-	-	N shore	20	89.4±2.7	86.2±2.6	-3.2	0.0005	0.08
cg24544876	-	-	S shore	5	78.3±3.3	75.1±2.5	-3.2	0.0008	0.08
cg14630692	*URM1*	Body	Open sea	9	86.4±1.7	83.2±2.4	-3.2	0.001	0.09
cg03440485	-	-	Island	X	22.9±2.3	19.7±2.1	-3.2	0.001	0.09
cg15832577‡	*C1orf53*	Body	S shore	1	78.6±2.5	75.3±3.2	-3.3	0.0002	0.07
cg17494438	*DRGX*	TSS1500	N shelf	10	82.6±1.8	79.2±2.8	-3.3	0.001	0.09
cg16320838	*DNAJB7*	TSS1500	Open sea	22	92.5±14.5	89.0±19.1	-3.5	0.0005	0.08
	XPNPEP3	Body							
cg11342670	*KIAA0319*	Body	Open sea	6	78.9±9.3	75.5±10.3	-3.5	0.001	0.09
cg03987985	*L1TD1*	3'UTR	Open sea	1	75.6±4.6	72.0±5.6	-3.6	0.001	0.09
cg08377570	*LPAR6*	TSS1500	Open	13	87.5±2.1	83.8±2.5	-3.7	0.0005	0.07

	RB1	Body	sea							596
cg17486639	-	-	N shelf	19	89.8±1.6	86.0±3.1	-3.8	0.0006	0.08	597
cg03834767	*CDK14*	3'UTR	Open	7	90.6±2.0	86.4±6.0	-4.1	0.002	0.09	598
			sea							599
cg16631698	-	-	Island	10	81.7±4.2	77.2±2.3	-4.5	0.002	0.09	600
cg08269188	*CBX5*	5'UTR	Open	12	83.7±2.7	79.0±4.5	-4.7	5.17×10^{-5}	0.06	601
			sea							602
cg05946920	*GGA1*	Body	Island	22	39.7±6.7	33.6±3.4	-6.2	0.002	0.096	603
										604

605 Data are expressed are beta values ± standard deviation.

606 Legend: Chr, chromosome number; Δ, difference; 3', three prime; 5', five prime; UTR, untranslated region; TSS1500, 1500 bases
607 upstream of transcription start site; TSS200, 200 bases upstream of transcription start site; *DMR, differentially methylated region;
608 †CDMR, cancer differentially methylated region; ‡RDMR, reprogrammed differentially methylated region.

609 Table 4. Molecular pathways related to genes with differentially methylated CpG

610 sites after exercise training ($p \leq 0.05$).

Pathway Name	**Enrichment Score**	***p*-value**	**# genes**	**Pathway ID**
Circadian entrainment	8.0	0.0003	24	kegg pathway 51
Axon guidance	7.2	0.001	29	kegg pathway 176
Endocytosis	7.0	0.001	39	kegg pathway 211
Glutamatergic synapse	6.1	0.002	25	kegg pathway 182
Protein digestion and absorption	5.9	0.003	22	kegg pathway 46
ECM-receptor interaction	5.4	0.004	19	kegg pathway 41
GABAergic synapse	4.7	0.01	22	kegg pathway 133
Bile secretion	4.4	0.01	18	kegg pathway 74
MAPK signaling pathway	4.4	0.01	41	kegg pathway 119
Focal adhesion	4.3	0.01	34	kegg pathway 5
PI3K-Akt signaling pathway	4.3	0.01	54	kegg pathway 45
Huntington's disease	4.3	0.01	33	kegg pathway 53
Transcriptional misregulation in cancer	4.3	0.01	31	kegg pathway 94
African trypanosomiasis	4.1	0.02	10	kegg pathway 69
Colorectal cancer	4.1	0.02	13	kegg pathway 148
Viral myocarditis	3.9	0.02	15	kegg pathway 105
Taurine and hypotaurine metabolism	3.7	0.02	4	kegg pathway 195
Galactose metabolism	3.7	0.03	8	kegg pathway 15

Long-term depression	3.6	0.03	12	kegg pathway 250
Endocrine and other factor-regulated calcium reabsorption	3.6	0.03	10	kegg pathway 258
Retrograde endocannabinoid signaling	3.6	0.03	21	kegg pathway 129
Glycosaminoglycan biosynthesis - chondroitin sulfate / dermatan sulfate	3.4	0.03	7	kegg pathway 248
Nicotine addiction	3.4	0.03	10	kegg pathway 62
Allograft rejection	3.4	0.03	10	kegg pathway 177
Selenocompound metabolism	3.4	0.04	5	kegg pathway 135
Morphine addiction	3.2	0.04	20	kegg pathway 86
Amoebiasis	3.2	0.04	21	kegg pathway 56
Graft-versus-host disease	3.1	0.04	10	kegg pathway 209
Maturity onset diabetes of the young	3.1	0.04	7	kegg pathway 241
Pathways in cancer	3.1	0.05	49	kegg pathway 128
ErbB signaling pathway	3.1	0.05	15	kegg pathway 121
Type I diabetes mellitus	2.9	0.05	10	kegg pathway 242
Insulin secretion	2.9	0.05	17	kegg pathway 4

611 Table 5. Paternally imprinted gene CpG methylation changes caused by exercise training.

		Location in relation to			***DNA methylation (%)***				
Paternally imprinted gene	**CpG site**	**Gene region**	**CpG island**	**Chr**	**Basal (mean±SD)**	**After exercise (mean±SD)**	**Δ**	***p*-value**	***q*-value (≤0.1)**
GRB10	cg12358041	5'UTR Body	Open sea	7	92.3±1.2	91.0±1.2	-1.3	0.0004	0.08
	cg26050906	5'UTR TSS200	Open sea	7	91.8±1.1	90.9±1.1	-0.9	0.003	0.10
SGCE PEG10	cg22090863*	Body TSS1500	N shore	7	4.0±0.6	4.6±0.6	0.7	0.0007	0.08
SGCE PEG10	cg18139769	TSS1500 5'UTR	S shore	7	10.5±2.0	13.5±4.5	3.0	0.0006	0.08
DLGAP2	cg27316067	Body	S shore	8	64.3±11.2	62.2±11.3	-2.1	0.002	0.09
SFMBT2	cg15362304	Body	S shelf	10	93.4±1.1	92.5±1.1	-0.9	0.0007	0.08
INS-IGF2	cg00273464	Body	Open sea	11	89.8±1.7	87.7±1.2	-2.0	0.00002	0.06

IGF2		1stExon 5'UTR							
INS-IGF2	cg17665927	Body	Open sea	11	93.2±1.3	91.6±1.4	-1.5	0.0002	0.07
IGF2		1stExon 5'UTR							
INS-IGF2	cg05384664	Body	S shore	11	88.6±2.2	87.3±2.8	-1.4	0.001	0.09
IGF2		Body							
KCNQ1OT1	cg20406758‡	Body	Open sea	11	95.5±1.0	94.1±1.0	-1.4	0.001	0.09
KCNQ1		Body							
SLC38A4	cg12152384	Body	Open sea	12	93.4±1.0	92.3±0.9	-1.1	0.002	0.09
WIF1	cg15862358	TSS1500	S shore	12	6.7±2.6	8.6±5.5	1.9	0.001	0.09
DLK1	cg17412258	TSS1500	CpG island	14	2.0±0.5	2.8±0.6	0.8	0.0005	0.08
	cg06504820	TSS1500	N shore	14	21.5±6.7	24.1±7.6	2.5	0.0003	0.07
RTL1	cg23546343	1stExon	N shore	14	93.0±0.9	91.8±1.0	-1.2	0.002	0.10
MIR431		TSS200							
MIR433		TSS1500							
GABRG3	cg08325929	Body	S shelf	15	86.2±2.5	84.9±2.7	-1.3	0.003	0.10

ZIM2	cg16008476	Body	N shore	19	5.9±1.6	7.6±2.7	1.7	0.0006	0.08
HM13	cg06000530	Body	CpG island	20	4.0±1.0	5.6±2.2	1.6	0.002	0.10
PSIMCT-1		TSS200							

Data are expressed are beta values ± standard deviation.

Legend: Chr, chromosome number; Δ, difference; 3', three prime; 5', five prime; UTR, untranslated region; TSS1500, 1500 bases upstream of transcription start site; TSS200, 200 bases upstream of transcription start site; *DMR, differentially methylated region; ‡RDMR, reprogrammed differentially methylated region.

626 Supplementary Table 1. Gene ontology for genes with DNA methylation changes after exercise training ($q \leq 0.1$).

Function	**Type**	**Enrichment score**	***p*-value**	***q*-value**	**# genes**	**Go ID**
Single-organism process	BP	34.82	7.57×10^{-16}	3.88×10^{-12}	1428	44699
Single-organism cellular process	BP	26.32	3.70×10^{-12}	9.50×10^{-9}	1251	44763
Biological process	BP	23.74	4.89×10^{-11}	8.22×10^{-8}	1968	8150
Cellular process	BP	23.47	6.41×10^{-11}	8.22×10^{-8}	1678	9987
Developmental process	BP	21.96	2.89×10^{-10}	2.97×10^{-7}	591	32502
Biological regulation	BP	19.53	3.31×10^{-9}	2.83×10^{-6}	1227	65007
Regulation of biological process	BP	18.66	7.88×10^{-9}	5.78×10^{-6}	1168	50789
Anatomical structure development	BP	18.31	1.12×10^{-8}	7.18×10^{-6}	374	48856
Anatomical structure morphogenesis	BP	17.79	1.87×10^{-8}	1.07×10^{-5}	213	9653

Cellular developmental process	BP	17.46	2.62×10^{-8}	1.29×10^{-5}	312	48869
Regulation of cellular process	BP	17.38	2.84×10^{-8}	1.29×10^{-5}	1113	50794
Single-organism developmental process	BP	17.32	3.01×10^{-8}	1.29×10^{-5}	405	44767
Ras guanyl-nucleotide exchange factor activity	MF	17.22	3.32×10^{-8}	1.31×10^{-5}	36	5088
Guanyl-nucleotide exchange factor activity	MF	17.04	3.97×10^{-8}	1.45×10^{-5}	50	5085
Gtpase regulator activity	MF	15.96	1.18×10^{-7}	4.02×10^{-5}	96	30695
Sequence-specific DNA binding transcription factor activity	MF	15.66	1.58×10^{-7}	4.68×10^{-5}	182	3700
Pattern specification process	BP	15.65	1.60×10^{-7}	4.68×10^{-5}	84	7389
Nucleic acid binding	MF	15.52	1.81×10^{-7}	4.68×10^{-5}	182	1071

transcription factor activity						
Small gtpase regulator activity	MF	15.52	1.82×10^{-7}	4.68×10^{-5}	71	5083
Ion binding	MF	15.49	1.88×10^{-7}	4.68×10^{-5}	867	43167
Nucleoside-triphosphatase regulator activity	MF	15.47	1.91×10^{-7}	4.68×10^{-5}	97	60589
Multicellular organismal process	BP	14.95	3.22×10^{-7}	7.51×10^{-5}	435	32501
Embryonic morphogenesis	BP	14.90	3.37×10^{-7}	7.51×10^{-5}	81	48598
Single-multicellular organism process	BP	14.75	3.91×10^{-7}	8.37×10^{-5}	428	44707
Molecular function	MF	14.47	5.18×10^{-7}	0.0001	2015	3674
Regulation of cell communication	BP	14.16	7.09×10^{-7}	0.0001	319	10646

Regulation of signaling	BP	14.14	7.22×10^{-7}	0.0001	318	23051
Regulation of cell development	BP	13.86	9.59×10^{-7}	0.0002	124	60284
Cell junction	CC	13.47	1.42×10^{-6}	0.0003	136	30054
Sequence-specific DNA binding	MF	13.17	1.90×10^{-6}	0.0003	127	43565
Binding	MF	12.88	2.55×10^{-6}	0.0004	1597	5488
Cell differentiation	BP	12.46	3.88×10^{-6}	0.0006	218	30154
Regulation of neurogenesis	BP	12.44	3.96×10^{-6}	0.0006	80	50767
Regionalization	BP	12.19	5.08×10^{-6}	0.0008	53	3002
Regulation of nervous system development	BP	12.16	5.24×10^{-6}	0.0008	87	51960
Negative regulation of cell differentiation	BP	11.75	7.85×10^{-6}	0.001	88	45596
Cellular response to stimulus	BP	11.54	9.69×10^{-6}	0.001	653	51716

Extracellular matrix	CC	11.31	1.22×10^{-5}	0.002	65	31012
Regulation of neuron differentiation	BP	11.27	1.28×10^{-5}	0.002	67	45664
Motor activity	MF	11.21	1.35×10^{-5}	0.002	34	3774
Extracellular matrix part	CC	11.21	1.35×10^{-5}	0.002	44	44420
Organ development	BP	11.20	1.37×10^{-5}	0.002	159	48513
Positive regulation of cellular process	BP	11.08	1.55×10^{-5}	0.002	471	48522
Regulation of cell differentiation	BP	10.78	2.08×10^{-5}	0.002	174	45595
Negative regulation of developmental process	BP	10.76	2.12×10^{-5}	0.002	103	51093
Positive regulation of cellular biosynthetic process	BP	10.76	2.13×10^{-5}	0.002	210	31328
Dendritic spine	CC	10.73	2.19×10^{-5}	0.002	18	43197
Synaptic transmission	BP	10.72	2.22×10^{-5}	0.002	81	7268

Neuron part	CC	10.65	2.36×10^{-5}	0.002	105	97458
System development	BP	10.60	2.50×10^{-5}	0.003	115	48731
Response to external stimulus	BP	10.57	2.57×10^{-5}	0.003	168	9605
Synapse part	CC	10.35	3.21×10^{-5}	0.003	71	44456
Cell communication	BP	10.34	3.22×10^{-5}	0.003	148	7154
Signal transduction	BP	10.33	3.26×10^{-5}	0.003	538	7165
Axon guidance	BP	10.31	3.32×10^{-5}	0.003	68	7411
Negative regulation of neuron differentiation	BP	10.15	3.91×10^{-5}	0.003	18	45665
Neuron spine	CC	10.15	3.91×10^{-5}	0.003	18	44309
Cation binding	MF	10.14	3.94×10^{-5}	0.003	581	43169
Metal ion binding	MF	10.07	4.23×10^{-5}	0.004	572	46872
Positive regulation of biosynthetic process	BP	10.06	4.26×10^{-5}	0.004	211	9891
Positive regulation of macromolecule	BP	10.05	4.33×10^{-5}	0.004	196	10557

biosynthetic process						
Regulation of signal transduction	BP	10.04	4.38×10^{-5}	0.004	271	9966
Phospholipid binding	MF	9.97	4.66×10^{-5}	0.004	93	5543
Ion channel activity	MF	9.89	5.05×10^{-5}	0.004	73	5216
Anterior/posterior pattern specification	BP	9.83	5.40×10^{-5}	0.004	36	9952
Substrate-specific channel activity	MF	9.68	6.24×10^{-5}	0.005	74	22838
Rho guanyl-nucleotide exchange factor activity	MF	9.61	6.69×10^{-5}	0.005	22	5089
Negative regulation of signal transduction	BP	9.56	7.04×10^{-5}	0.005	110	9968
Cell part	CC	9.55	7.10×10^{-5}	0.005	1907	44464
Negative regulation of response to stimulus	BP	9.48	7.66×10^{-5}	0.006	131	48585
Positive regulation of	BP	9.45	7.84×10^{-5}	0.006	194	45935

nucleobase-containing compound metabolic process						
Regulation of axon extension involved in axon guidance	BP	9.42	8.13×10^{-5}	0.006	7	48841
Negative regulation of biological process	BP	9.26	9.50×10^{-5}	0.007	456	48519
Regulation of small gtpase mediated signal transduction	BP	9.26	9.55×10^{-5}	0.007	56	51056
Regulation of purine nucleotide metabolic process	BP	9.24	9.69×10^{-5}	0.007	72	1900542
Cell development	BP	9.12	0.0001	0.007	79	48468
Negative regulation of cell communication	BP	9.04	0.0001	0.008	114	10648

Gated channel activity	MF	9.03	0.0001	0.008	60	22836
Ion gated channel activity	MF	9.03	0.0001	0.008	60	22839
DNA binding	MF	9.00	0.0001	0.008	351	3677
Response to stimulus	BP	8.99	0.0001	0.008	827	50896
Positive regulation of nitrogen compound metabolic process	BP	8.94	0.0001	0.008	196	51173
Regulation of nucleotide metabolic process	BP	8.91	0.0001	0.008	72	6140
Channel activity	MF	8.88	0.0001	0.008	76	15267
Passive transmembrane transporter activity	MF	8.88	0.0001	0.008	76	22803
Organ morphogenesis	BP	8.80	0.0002	0.009	76	9887
Extracellular matrix disassembly	BP	8.78	0.0002	0.009	22	22617
Negative regulation of	BP	8.74	0.0002	0.009	113	23057

signaling						
Negative regulation of cellular process	BP	8.67	0.0002	0.01	421	48523
Neuron projection	CC	8.64	0.0002	0.01	80	43005
Cell projection part	CC	8.61	0.0002	0.01	111	44463
Positive regulation of cellular metabolic process	BP	8.61	0.0002	0.01	292	31325
Positive regulation of RNA metabolic process	BP	8.52	0.0002	0.01	173	51254
Regulation of cellular component organization	BP	8.51	0.0002	0.01	202	51128
Intracellular part	CC	8.51	0.0002	0.01	1607	44424
Enzyme regulator activity	MF	8.51	0.0002	0.01	161	30234
Positive regulation of metabolic process	BP	8.48	0.0002	0.01	306	9893

Regulation of Ras protein signal transduction	BP	8.45	0.0002	0.01	35	46578
Regulation of multicellular organismal process	BP	8.45	0.0002	0.01	275	51239
Cation channel activity	MF	8.40	0.0002	0.01	54	5261
Negative regulation of canonical Wnt receptor signaling pathway	BP	8.39	0.0002	0.01	22	90090
Collagen metabolic process	BP	8.39	0.0002	0.01	22	32963
Plasma membrane part	CC	8.38	0.0002	0.01	284	44459
Collagen	CC	8.37	0.0002	0.01	24	5581
Locomotion	BP	8.34	0.0002	0.01	159	40011
Regulation of multicellular organismal	BP	8.27	0.0003	0.01	178	2000026

development						
Regulation of Wnt receptor signaling pathway	BP	8.25	0.0003	0.01	40	30111
Collagen catabolic process	BP	8.25	0.0003	0.01	20	30574
Multicellular organismal metabolic process	BP	8.20	0.0003	0.01	24	44236
Regulation of localization	BP	8.14	0.0003	0.01	214	32879
Connective tissue development	BP	8.08	0.0003	0.01	26	61448
Positive regulation of transcription, DNA-dependent	BP	8.07	0.0003	0.01	164	45893
Positive regulation of gtpase activity	BP	8.06	0.0003	0.01	34	43547

Positive regulation of macromolecule metabolic process	BP	7.97	0.0003	0.02	284	10604
Neuron fate commitment	BP	7.96	0.0004	0.02	11	48663
Ionotropic glutamate receptor complex	CC	7.96	0.0004	0.02	11	8328
Synaptic membrane	CC	7.95	0.0004	0.02	45	97060
Multicellular organismal catabolic process	BP	7.93	0.0004	0.02	21	44243
Ion transmembrane transporter activity	MF	7.90	0.0004	0.02	127	15075
Cellular component organization	BP	7.86	0.0004	0.02	491	16043
Establishment of localization	BP	7.84	0.0004	0.02	427	51234
Embryonic placenta development	BP	7.84	0.0004	0.02	10	1892

Localization	BP	7.84	0.0004	0.02	71	51179
Tissue development	BP	7.83	0.0004	0.02	96	9888
Regulation of canonical Wnt receptor signaling pathway	BP	7.68	0.0005	0.02	30	60828
Energy reserve metabolic process	BP	7.67	0.0005	0.02	32	6112
Regulation of cellular component biogenesis	BP	7.67	0.0005	0.02	68	44087
Membrane-bounded vesicle	CC	7.66	0.0005	0.02	104	31988
Intracellular signal transduction	BP	7.65	0.0005	0.02	206	35556
Regulation of Rho protein signal transduction	BP	7.59	0.0005	0.02	23	35023
Axis specification	BP	7.52	0.0005	0.02	18	9798

Ion channel complex	CC	7.50	0.0006	0.02	41	34702
Microtubule motor activity	MF	7.48	0.0006	0.02	20	3777
Signaling	BP	7.46	0.0006	0.02	118	23052
Single organism signaling	BP	7.46	0.0006	0.02	118	44700
Negative regulation of Wnt receptor signaling pathway	BP	7.44	0.0006	0.02	27	30178
Embryonic organ morphogenesis	BP	7.44	0.0006	0.02	27	48562
Cell-cell signaling	BP	7.44	0.0006	0.02	115	7267
Positive regulation of gene expression	BP	7.39	0.0006	0.02	174	10628
Multicellular organismal macromolecule metabolic process	BP	7.32	0.0007	0.02	22	44259

Establishment or maintenance of cell polarity	BP	7.32	0.0007	0.02	22	7163
Regulation of developmental growth	BP	7.32	0.0007	0.02	26	48638
Lipid binding	MF	7.30	0.0007	0.02	123	8289
Regulation of cell proliferation	BP	7.29	0.0007	0.02	183	42127
Substrate-specific transmembrane transporter activity	MF	7.22	0.0007	0.03	134	22891
Regulation of developmental process	BP	7.21	0.0007	0.03	223	50793
Taxis	BP	7.16	0.0008	0.03	92	42330
Chemotaxis	BP	7.16	0.0008	0.03	92	6935
Ligand-gated ion channel activity	MF	7.15	0.0008	0.03	30	15276

Ligand-gated channel activity	MF	7.15	0.0008	0.03	30	22834
Cell fate determination	BP	7.15	0.0008	0.03	13	1709
Vesicle	CC	7.13	0.0008	0.03	116	31982
Negative regulation of cell development	BP	7.02	0.0009	0.03	27	10721
Wnt receptor signaling pathway	BP	7.02	0.0009	0.03	44	16055
Cellular component organization or biogenesis	BP	7.02	0.0009	0.03	491	71840
Positive regulation of biological process	BP	7.00	0.0009	0.03	513	48518
Membrane	CC	6.94	0.0010	0.03	801	16020
Regulation of metabolic process	BP	6.92	0.0010	0.03	672	19222
Positive regulation of	BP	6.90	0.0010	0.03	118	45944

transcription from RNA polymerase II promoter						
Negative regulation of axonogenesis	BP	6.90	0.0010	0.03	13	50771
Regulation of respiratory gaseous exchange	BP	6.89	0.0010	0.03	8	43576
Transport	BP	6.87	0.0010	0.03	416	6810
Transport vesicle membrane	CC	6.86	0.0011	0.03	17	30658
Energy derivation by oxidation of organic compounds	BP	6.85	0.0011	0.03	37	15980
Positive regulation of cell development	BP	6.84	0.0011	0.03	33	10720
Regulation of cell adhesion	BP	6.82	0.0011	0.03	51	30155
Actin filament-based	BP	6.82	0.0011	0.03	54	30029

process						
Cell surface receptor signaling pathway	BP	6.81	0.0011	0.03	312	7166
Cell-cell junction	CC	6.79	0.0011	0.03	52	5911
Activation of Ras gtpase activity	BP	6.79	0.0011	0.03	10	32856
Chromatin binding	MF	6.73	0.0012	0.04	62	3682
Tissue morphogenesis	BP	6.72	0.0012	0.04	63	48729
Regulation of nucleobase-containing compound metabolic process	BP	6.70	0.0012	0.04	487	19219
Negative regulation of neurogenesis	BP	6.69	0.0012	0.04	22	50768
Microtubule associated complex	CC	6.64	0.0013	0.04	29	5875
Transcription, DNA-	BP	6.59	0.0014	0.04	308	6351

dependent						
Early endosome membrane	CC	6.57	0.0014	0.04	21	31901
Cation channel complex	CC	6.52	0.0015	0.04	29	34703
Positive regulation of neurogenesis	BP	6.49	0.0015	0.04	26	50769
Coated vesicle membrane	CC	6.49	0.0015	0.04	25	30662
Columnar/cuboidal epithelial cell development	BP	6.42	0.0016	0.05	7	2066
Regulation of steroid biosynthetic process	BP	6.42	0.0016	0.05	13	50810
ER to Golgi transport vesicle membrane	CC	6.42	0.0016	0.05	11	12507
Dynein complex	CC	6.40	0.0017	0.05	12	30286
Positive regulation of	BP	6.40	0.0017	0.05	88	51130

cellular component organization						
Site of polarized growth	CC	6.39	0.0017	0.05	22	30427
Skeletal system morphogenesis	BP	6.37	0.0017	0.05	23	48705
Negative regulation of intracellular protein kinase cascade	BP	6.37	0.0017	0.05	23	10741
Common myeloid progenitor cell proliferation	BP	6.33	0.0018	0.05	3	35726
Regulation of somitogenesis	BP	6.33	0.0018	0.05	3	14807
Detection of monosaccharide stimulus	BP	6.33	0.0018	0.05	3	34287
Detection of glucose	BP	6.33	0.0018	0.05	3	51594

Detection of carbohydrate stimulus	BP	6.33	0.0018	0.05	3	9730
Detection of hexose stimulus	BP	6.33	0.0018	0.05	3	9732
Insulin-like growth factor-activated receptor activity	MF	6.33	0.0018	0.05	3	5010
Laminin-10 complex	CC	6.33	0.0018	0.05	3	43259
Cell projection	CC	6.26	0.0019	0.05	139	42995
Multicellular organismal development	BP	6.25	0.0019	0.05	81	7275
Positive regulation of Ras gtpase activity	BP	6.23	0.0020	0.05	23	32320
Endoplasmic reticulum part	CC	6.22	0.0020	0.05	142	44432
Regulation of GTP catabolic process	BP	6.21	0.0020	0.05	44	33124

Regulation of nitrogen compound metabolic process	BP	6.20	0.0020	0.05	495	51171
Neuron recognition	BP	6.19	0.0020	0.05	10	8038
Negative regulation of cell proliferation	BP	6.17	0.0021	0.05	88	8285
Regulation of cellular metabolic process	BP	6.16	0.0021	0.05	612	31323
Negative regulation of axon extension involved in axon guidance	BP	6.14	0.0022	0.05	5	48843
Negative regulation of JAK-STAT cascade	BP	6.14	0.0022	0.05	5	46426
N-methyl-D-aspartate selective glutamate receptor complex	CC	6.14	0.0022	0.05	5	17146
Regulation of	BP	6.10	0.0022	0.05	22	50770

axonogenesis						
Neuron differentiation	BP	6.09	0.0023	0.06	38	30182
Cytoskeleton organization	BP	6.05	0.0024	0.06	93	7010
Regulation of growth	BP	6.05	0.0024	0.06	85	40008
Regulation of nucleoside metabolic process	BP	6.01	0.0025	0.06	48	9118
Establishment of protein localization to membrane	BP	5.98	0.0025	0.06	9	90150
Integral to endoplasmic reticulum membrane	CC	5.97	0.0025	0.06	21	30176
Growth cone	CC	5.97	0.0025	0.06	21	30426
Cartilage development involved in endochondral bone	BP	5.97	0.0025	0.06	6	60351

morphogenesis						
Enzyme linked receptor protein signaling pathway	BP	5.96	0.0026	0.06	112	7167
Intramembranous ossification	BP	5.93	0.0027	0.06	4	1957
Direct ossification	BP	5.93	0.0027	0.06	4	36072
Regulation of transport	BP	5.91	0.0027	0.06	157	51049
Embryonic skeletal system morphogenesis	BP	5.90	0.0027	0.06	18	48704
Regulation of catabolic process	BP	5.90	0.0027	0.06	88	9894
Regulation of gtpase activity	BP	5.90	0.0027	0.06	43	43087
Transmembrane receptor protein tyrosine kinase signaling	BP	5.90	0.0028	0.06	87	7169

pathway						
Extracellular vesicular exosome	CC	5.85	0.0029	0.07	16	70062
Antigen processing and presentation of exogenous peptide antigen via MHC class II	BP	5.83	0.0029	0.07	21	19886
Tight junction	CC	5.83	0.0029	0.07	23	5923
Occluding junction	CC	5.83	0.0029	0.07	23	70160
Serine-type endopeptidase inhibitor activity	MF	5.83	0.0029	0.07	22	4867
Cellular component movement	BP	5.83	0.0029	0.07	138	6928
Membrane-enclosed lumen	CC	5.78	0.0031	0.07	101	31974
Vesicle membrane	CC	5.77	0.0031	0.07	61	12506

Regulatory region nucleic acid binding	MF	5.77	0.0031	0.07	62	1067
Regulatory region DNA binding	MF	5.77	0.0031	0.07	62	975
Regulation of primary metabolic process	BP	5.76	0.0031	0.07	601	80090
Regulation of purine nucleotide catabolic process	BP	5.72	0.0033	0.07	47	33121
Cartilage development	BP	5.72	0.0033	0.07	19	51216
Response to glucagon stimulus	BP	5.71	0.0033	0.07	12	33762
Regulation of anatomical structure morphogenesis	BP	5.70	0.0034	0.07	98	22603
Cytoplasmic vesicle membrane	CC	5.65	0.0035	0.07	59	30659

Regulation of biological quality	BP	5.65	0.0035	0.07	314	65008
Regulation of nucleotide catabolic process	BP	5.64	0.0035	0.07	47	30811
Metal ion transmembrane transporter activity	MF	5.64	0.0036	0.08	65	46873
Ionotropic glutamate receptor activity	MF	5.62	0.0036	0.08	7	4970
Cell motility	BP	5.60	0.0037	0.08	102	48870
Regulation of stress-activated MAPK cascade	BP	5.60	0.0037	0.08	31	32872
Single-organism transport	BP	5.59	0.0037	0.08	323	44765
Regulation of cellular localization	BP	5.58	0.0038	0.08	111	60341

Antigen processing and presentation of peptide antigen via MHC class II	BP	5.56	0.0038	0.08	21	2495
Response to endogenous stimulus	BP	5.56	0.0039	0.08	156	9719
Actin cytoskeleton organization	BP	5.55	0.0039	0.08	44	30036
Anchoring collagen	CC	5.55	0.0039	0.08	5	30934
Axonal growth cone	CC	5.55	0.0039	0.08	5	44295
Mannose metabolic process	BP	5.55	0.0039	0.08	5	6013
Semaphorin-plexin signaling pathway	BP	5.52	0.0040	0.08	6	71526
Biological adhesion	BP	5.52	0.0040	0.08	121	22610
Cell adhesion	BP	5.52	0.0040	0.08	121	7155
Extracellular organelle	CC	5.51	0.0040	0.08	16	43230
Extracellular membrane-	CC	5.51	0.0040	0.08	16	65010

bounded organelle						
Regulation of stress-activated protein kinase signaling cascade	BP	5.50	0.0041	0.08	31	70302
Positive regulation of insulin secretion	BP	5.50	0.0041	0.08	12	32024
Macromolecule localization	BP	5.47	0.0042	0.08	57	33036
Intrinsic to endoplasmic reticulum membrane	CC	5.46	0.0043	0.08	23	31227
Homeostatic process	BP	5.45	0.0043	0.08	152	42592
Transmembrane transporter activity	MF	5.44	0.0043	0.08	141	22857
Endocytosis	BP	5.44	0.0044	0.08	46	6897
Negative regulation of cell adhesion	BP	5.43	0.0044	0.08	20	7162
Integral to lumenal side	CC	5.41	0.0045	0.09	9	71556

of endoplasmic reticulum membrane						
Embryonic skeletal system development	BP	5.41	0.0045	0.09	10	48706
Protein binding	MF	5.40	0.0045	0.09	965	5515
Small gtpase mediated signal transduction	BP	5.36	0.0047	0.09	71	7264
Regulation of steroid metabolic process	BP	5.35	0.0047	0.09	16	19218
Secretion by cell	BP	5.33	0.0048	0.09	63	32940
Liver development	BP	5.32	0.0049	0.09	17	1889
Antigen processing and presentation of peptide or polysaccharide antigen via MHC class II	BP	5.30	0.0050	0.09	21	2504
Epithelial tube morphogenesis	BP	5.29	0.0050	0.09	19	60562

Regulation of response to stimulus	BP	5.28	0.0051	0.09	348	48583
Gtpase activator activity	MF	5.27	0.0051	0.09	47	5096
Organelle	CC	5.27	0.0051	0.09	1126	43226
Extracellular-glutamate-gated ion channel activity	MF	5.27	0.0051	0.09	7	5234
Osteoblast development	BP	5.27	0.0051	0.09	7	2076
Adherens junction	CC	5.25	0.0053	0.10	37	5912
Cardiac septum morphogenesis	BP	5.22	0.0054	0.10	11	60411
Cation transmembrane transporter activity	MF	5.22	0.0054	0.10	94	8324
Secretion	BP	5.22	0.0054	0.10	75	46903
Regulation of insulin secretion	BP	5.21	0.0054	0.10	29	50796
Regulation of peptide	BP	5.21	0.0055	0.10	31	90276

hormone secretion						
Regulation of hormone secretion	BP	5.19	0.0056	0.10	36	46883
Dorsal spinal cord development	BP	5.19	0.0056	0.10	4	21516
Peripheral nervous system myelin maintenance	BP	5.19	0.0056	0.10	4	32287
Positive regulation of superoxide anion generation	BP	5.19	0.0056	0.10	4	32930
Lipid particle organization	BP	5.19	0.0056	0.10	4	34389
Morphogenesis of an epithelium	BP	5.17	0.0057	0.10	50	2009
Positive regulation of hormone secretion	BP	5.17	0.0057	0.10	17	46887

Establishment of protein localization to plasma membrane	BP	5.17	0.0057	0.10	8	90002
Rab guanyl-nucleotide exchange factor activity	MF	5.17	0.0057	0.10	8	17112
Negative regulation of osteoblast differentiation	BP	5.17	0.0057	0.10	10	45668
Response to chemical stimulus	BP	5.16	0.0057	0.10	366	42221
Ras gtpase activator activity	MF	5.16	0.0057	0.10	25	5099
Response to nitrogen compound	BP	5.15	0.0058	0.10	96	1901698
Axonogenesis	BP	5.13	0.0059	0.10	24	7409
Regulation of JNK cascade	BP	5.13	0.0059	0.10	27	46328
Substrate-specific	MF	5.12	0.0059	0.10	146	22892

transporter activity						
Positive regulation of cell differentiation	BP	5.12	0.0060	0.10	81	45597
Cytoplasmic membrane-bounded vesicle	CC	5.11	0.0060	0.10	89	16023
RNA biosynthetic process	BP	5.11	0.0061	0.10	323	32774
Regulation of secretion	BP	5.10	0.0061	0.10	74	51046
Regulation of cell-substrate adhesion	BP	5.10	0.0061	0.10	23	10810
Neuropeptide receptor activity	MF	5.10	0.0061	0.10	12	8188
Establishment of cell polarity	BP	5.10	0.0061	0.10	12	30010
Cellular component morphogenesis	BP	5.09	0.0061	0.10	63	32989
Cell fate commitment	BP	5.09	0.0062	0.10	26	45165

Positive regulation of secretion	BP	5.09	0.0062	0.10	40	51047
Golgi apparatus part	CC	5.07	0.0063	0.10	103	44431
Response to organic nitrogen	BP	5.05	0.0064	0.10	92	10243
Regulation of sequestering of triglyceride	BP	5.05	0.0064	0.10	5	10889
Platelet-derived growth factor binding	MF	5.05	0.0064	0.10	5	48407
MHC class II receptor activity	MF	5.05	0.0064	0.10	5	32395
Positive regulation of neuron differentiation	BP	5.04	0.0065	0.10	16	45666
Small conductance calcium-activated potassium channel	MF	5.04	0.0065	0.10	3	16286

activity						
Cardiac endothelial cell differentiation	BP	5.04	0.0065	0.10	3	3348
Endocardial cell differentiation	BP	5.04	0.0065	0.10	3	60956
N-acetylgalactosaminyl-proteoglycan 3-beta-glucuronosyltransferase activity	MF	5.04	0.0065	0.10	3	50510
Positive regulation of transcription of Notch receptor target	BP	5.04	0.0065	0.10	3	7221
Glossopharyngeal nerve morphogenesis	BP	5.04	0.0065	0.10	3	21615
Extracellular matrix-cell signaling	BP	5.04	0.0065	0.10	3	35426
Immunoglobulin	BP	5.04	0.0065	0.10	3	2381

production involved in immunoglobulin mediated immune response						
Nerve growth factor processing	BP	5.04	0.0065	0.10	3	32455
Enzyme binding	MF	5.04	0.0065	0.10	162	19899
Cell recognition	BP	5.03	0.0066	0.10	17	8037
Regulation of peptide secretion	BP	5.02	0.0066	0.10	31	2791
Regulation of peptide transport	BP	5.02	0.0066	0.10	31	90087
Cytoplasmic vesicle part	CC	4.99	0.0068	0.10	73	44433
Skeletal system development	BP	4.97	0.0069	0.11	30	1501
Postsynaptic membrane	CC	4.97	0.0070	0.11	35	45211
Postsynaptic density	CC	4.96	0.0070	0.11	22	14069

Bone morphogenesis	BP	4.95	0.0071	0.11	7	60349
Synaptic transmission, glutamatergic	BP	4.95	0.0071	0.11	7	35249
Cortical actin cytoskeleton	CC	4.95	0.0071	0.11	7	30864
Cellular response to glucagon stimulus	BP	4.95	0.0071	0.11	10	71377
Negative regulation of growth	BP	4.94	0.0071	0.11	36	45926
Regulation of transcription from RNA polymerase II promoter	BP	4.92	0.0073	0.11	185	6357
Embryonic digit morphogenesis	BP	4.91	0.0074	0.11	12	42733
Regulation of extent of cell growth	BP	4.91	0.0074	0.11	12	61387
Potassium channel	CC	4.90	0.0075	0.11	16	34705

complex						
Voltage-gated potassium channel complex	CC	4.90	0.0075	0.11	16	8076
Regulation of JAK-STAT cascade	BP	4.90	0.0075	0.11	16	46425
Regulation of phosphorus metabolic process	BP	4.88	0.0076	0.11	186	51174
Gland development	BP	4.84	0.0079	0.12	22	48732
Anion binding	MF	4.84	0.0079	0.12	380	43168
Regulation of membrane potential	BP	4.83	0.0080	0.12	34	42391
Regulation of phosphate metabolic process	BP	4.81	0.0081	0.12	184	19220
Epithelial cell development	BP	4.80	0.0082	0.12	24	2064

Embryonic heart tube morphogenesis	BP	4.79	0.0083	0.12	14	3143
Inner ear morphogenesis	BP	4.79	0.0083	0.12	14	42472
Regulation of vesicle-mediated transport	BP	4.79	0.0084	0.12	40	60627
Clathrin-coated vesicle membrane	CC	4.77	0.0085	0.12	19	30665
Cell migration	BP	4.77	0.0085	0.12	91	16477
Central nervous system neuron differentiation	BP	4.77	0.0085	0.12	15	21953
Negative regulation of axon extension	BP	4.75	0.0086	0.12	6	30517
Protein kinase C activity	MF	4.75	0.0086	0.12	6	4697
Regulation of cellular catabolic process	BP	4.75	0.0086	0.12	75	31329
Response to growth	BP	4.75	0.0086	0.12	83	70848

factor stimulus						
Organic substance biosynthetic process	BP	4.75	0.0087	0.12	500	1901576
L-amino acid transmembrane transporter activity	MF	4.73	0.0088	0.12	10	15179
Embryo implantation	BP	4.73	0.0088	0.12	10	7566
Endocytic vesicle membrane	CC	4.73	0.0088	0.12	22	30666
Glycogen metabolic process	BP	4.73	0.0088	0.12	12	5977
Transcription-coupled nucleotide-excision repair	BP	4.73	0.0088	0.12	12	6283
Neuron projection morphogenesis	BP	4.72	0.0089	0.12	32	48812
Epidermis development	BP	4.69	0.0092	0.13	28	8544

Regulation of actin filament-based process	BP	4.68	0.0093	0.13	37	32970
Cellular response to growth factor stimulus	BP	4.68	0.0093	0.13	81	71363
Response to nicotine	BP	4.67	0.0094	0.13	9	35094
Midbrain development	BP	4.67	0.0094	0.13	9	30901
Cell body	CC	4.67	0.0094	0.13	44	44297
Positive regulation of peptide hormone secretion	BP	4.67	0.0094	0.13	13	90277
G-protein coupled receptor signaling pathway	BP	4.67	0.0094	0.13	84	7186
Cellular nitrogen compound biosynthetic process	BP	4.66	0.0095	0.13	366	44271
Pancreas development	BP	4.65	0.0095	0.13	7	31016

Ventricular septum morphogenesis	BP	4.65	0.0095	0.13	7	60412
Protein localization	BP	4.65	0.0096	0.13	51	8104
Regulation of actin cytoskeleton organization	BP	4.64	0.0096	0.13	35	32956
Regulation of cyclic nucleotide metabolic process	BP	4.64	0.0096	0.13	25	30799
Binding, bridging	MF	4.64	0.0097	0.13	27	60090
Neuronal cell body	CC	4.64	0.0097	0.13	40	43025
Canonical Wnt receptor signaling pathway	BP	4.62	0.0099	0.13	17	60070
Atrial septum morphogenesis	BP	4.61	0.0099	0.13	5	60413
Outer membrane-bounded periplasmic	CC	4.61	0.0099	0.13	5	30288

space						
Periplasmic space	CC	4.61	0.0099	0.13	5	42597
Detection of bacterium	BP	4.61	0.0099	0.13	5	16045
Endocytic recycling	BP	4.61	0.0099	0.13	5	32456
Microtubule	CC	4.61	0.01	0.13	58	5874
Positive regulation of transport	BP	4.61	0.01	0.13	79	51050
Hepatocyte differentiation	BP	4.59	0.01	0.13	4	70365
Glomerular visceral epithelial cell development	BP	4.59	0.01	0.13	4	72015
Hydrogen peroxide biosynthetic process	BP	4.59	0.01	0.13	4	50665
RNA-induced silencing complex	CC	4.59	0.01	0.13	4	16442
Rnai effector complex	CC	4.59	0.01	0.13	4	31332

Regulation of dendritic cell antigen processing and presentation	BP	4.59	0.01	0.13	4	2604
Left/right axis specification	BP	4.59	0.01	0.13	4	70986
CARD domain binding	MF	4.59	0.01	0.13	4	50700
Neuron migration	BP	4.59	0.01	0.13	21	1764
Cellular localization	BP	4.59	0.01	0.13	49	51641
Regulation of cell morphogenesis involved in differentiation	BP	4.59	0.01	0.13	34	10769
Regulation of cellular component movement	BP	4.58	0.01	0.13	73	51270
Glucan metabolic process	BP	4.55	0.01	0.13	12	44042
Cellular glucan metabolic process	BP	4.55	0.01	0.13	12	6073

Brain development	BP	4.55	0.01	0.13	32	7420
Transcription regulatory region DNA binding	MF	4.55	0.01	0.13	58	44212
Cell proliferation	BP	4.55	0.01	0.13	88	8283
Regulation of interleukin-1 beta production	BP	4.53	0.01	0.13	10	32651
Biosynthetic process	BP	4.52	0.01	0.13	507	9058
Cytoplasmic vesicle	CC	4.51	0.01	0.14	97	31410
Positive regulation of peptide secretion	BP	4.51	0.01	0.14	13	2793
Positive regulation of cytokine biosynthetic process	BP	4.49	0.01	0.14	14	42108
Appendage morphogenesis	BP	4.48	0.01	0.14	21	35107
Limb morphogenesis	BP	4.48	0.01	0.14	21	35108

Embryonic forelimb morphogenesis	BP	4.45	0.01	0.14	9	35115
Tight junction assembly	BP	4.45	0.01	0.14	9	70830
Positive regulation of cell adhesion	BP	4.45	0.01	0.14	25	45785
Cellular response to acid	BP	4.44	0.01	0.14	11	71229
Golgi membrane	CC	4.43	0.01	0.14	80	139
Asymmetric protein localization	BP	4.42	0.01	0.14	6	8105
Positive regulation of developmental process	BP	4.42	0.01	0.14	106	51094
Neuron development	BP	4.41	0.01	0.15	22	48666
Potassium channel activity	MF	4.41	0.01	0.15	22	5267
Regulation of camp metabolic process	BP	4.41	0.01	0.15	22	30814

Cytoplasmic part	CC	4.40	0.01	0.15	888	44444
Intrinsic to plasma membrane	CC	4.40	0.01	0.15	156	31226
Coated vesicle	CC	4.40	0.01	0.15	26	30135
Clathrin-coated vesicle	CC	4.40	0.01	0.15	24	30136
Negative regulation of developmental growth	BP	4.40	0.01	0.15	8	48640
Insulin-like growth factor binding	MF	4.40	0.01	0.15	8	5520
Regulation of locomotion	BP	4.39	0.01	0.15	73	40012
Intracellular organelle	CC	4.39	0.01	0.15	1114	43229
Cellular response to vascular endothelial growth factor stimulus	BP	4.38	0.01	0.15	7	35924
Positive regulation of epithelial to	BP	4.38	0.01	0.15	7	10718

mesenchymal transition						
DNA-dependent transcription, initiation	BP	4.37	0.01	0.15	38	6352
Calcium channel activity	MF	4.37	0.01	0.15	21	5262
Lung development	BP	4.36	0.01	0.15	17	30324
Regulation of gliogenesis	BP	4.34	0.01	0.15	14	14013
Regulation of axon extension	BP	4.34	0.01	0.15	10	30516
Positive regulation of cyclase activity	BP	4.34	0.01	0.15	10	31281
Aromatic compound biosynthetic process	BP	4.34	0.01	0.15	355	19438
Organic cyclic compound biosynthetic process	BP	4.32	0.01	0.15	370	1901362
Organelle lumen	CC	4.32	0.01	0.15	90	43233

Cellular_component	CC	4.30	0.01	0.15	2166	5575
Aminoglycan metabolic process	BP	4.30	0.01	0.15	29	6022
Digestive tract development	BP	4.27	0.01	0.16	11	48565
Cortical cytoskeleton	CC	4.27	0.01	0.16	11	30863
Inorganic cation transmembrane transporter activity	MF	4.26	0.01	0.16	74	22890
Anterior/posterior axis specification	BP	4.25	0.01	0.16	9	9948
Cytoskeleton	CC	4.23	0.01	0.16	106	5856
Cellular membrane organization	BP	4.23	0.01	0.16	64	16044
Plasma membrane	CC	4.23	0.01	0.16	488	5886
Dopaminergic neuron differentiation	BP	4.23	0.01	0.16	5	71542

Regulation of respiratory gaseous exchange by neurological system process	BP	4.23	0.01	0.16	5	2087
Positive regulation of Wnt receptor signaling pathway	BP	4.22	0.01	0.16	16	30177
Phosphoglucomutase activity	MF	4.22	0.01	0.16	3	4614
Microvillus assembly	BP	4.22	0.01	0.16	3	30033
Microvillus organization	BP	4.22	0.01	0.16	3	32528
Noradrenergic neuron differentiation	BP	4.22	0.01	0.16	3	3357
Positive regulation of Wnt receptor signaling pathway, planar cell polarity pathway	BP	4.22	0.01	0.16	3	2000096

Response to oleic acid	BP	4.22	0.01	0.16	3	34201
Chemorepellent activity	MF	4.22	0.01	0.16	3	45499
Positive regulation of steroid hormone biosynthetic process	BP	4.22	0.01	0.16	3	90031
Membrane-bounded organelle	CC	4.19	0.02	0.17	1000	43227
Generation of precursor metabolites and energy	BP	4.17	0.02	0.17	63	6091
Non-canonical Wnt receptor signaling pathway	BP	4.17	0.02	0.17	8	35567
Microtubule-based movement	BP	4.16	0.02	0.17	28	7018
Heterocycle biosynthetic process	BP	4.16	0.02	0.17	354	18130
Nucleobase-containing	BP	4.15	0.02	0.17	345	34654

compound biosynthetic process						
Glycogen biosynthetic process	BP	4.13	0.02	0.17	6	5978
Glucan biosynthetic process	BP	4.13	0.02	0.17	6	9250
Cell differentiation in hindbrain	BP	4.13	0.02	0.17	6	21533
MHC class II protein complex	CC	4.13	0.02	0.17	6	42613
Regulation of timing of cell differentiation	BP	4.11	0.02	0.17	4	48505
Glomerular epithelial cell development	BP	4.11	0.02	0.17	4	72310
Negative regulation of catenin import into nucleus	BP	4.11	0.02	0.17	4	35414

Negative regulation of smooth muscle cell differentiation	BP	4.11	0.02	0.17	4	51151
Pinocytosis	BP	4.11	0.02	0.17	4	6907
Semaphorin receptor activity	MF	4.11	0.02	0.17	4	17154
RNA polymerase II core binding	MF	4.11	0.02	0.17	4	993
Regulation of glial cell differentiation	BP	4.10	0.02	0.17	11	45685
Regulation of stem cell proliferation	BP	4.10	0.02	0.18	16	72091
Extracellular matrix organization	BP	4.09	0.02	0.18	43	30198
Regulation of DNA binding	BP	4.08	0.02	0.18	15	51101
Organic cyclic	MF	4.07	0.02	0.18	721	97159

compound binding						
Regulation of chemokine production	BP	4.07	0.02	0.18	12	32642
Phagocytic vesicle membrane	CC	4.07	0.02	0.18	12	30670
Palate development	BP	4.06	0.02	0.18	14	60021
Regulation of cyclase activity	BP	4.06	0.02	0.18	14	31279
Cellular biosynthetic process	BP	4.06	0.02	0.18	482	44249
Positive regulation of gliogenesis	BP	4.05	0.02	0.18	9	14015
Tissue homeostasis	BP	4.04	0.02	0.18	18	1894
Regulation of cell projection organization	BP	4.03	0.02	0.18	44	31344
Extracellular structure organization	BP	4.02	0.02	0.18	43	43062

Actin binding	MF	4.01	0.02	0.19	58	3779
Endosome membrane	CC	4.00	0.02	0.19	51	10008
Regulation of cell growth	BP	3.98	0.02	0.19	48	1558
Positive regulation of lyase activity	BP	3.98	0.02	0.19	10	51349
Response to fatty acid	BP	3.98	0.02	0.19	10	70542
Regulation of epithelial to mesenchymal transition	BP	3.98	0.02	0.19	10	10717
Tube morphogenesis	BP	3.97	0.02	0.19	19	35239
Macromolecule biosynthetic process	BP	3.97	0.02	0.19	384	9059
Embryo development ending in birth or egg hatching	BP	3.97	0.02	0.19	37	9792
Growth factor binding	MF	3.96	0.02	0.19	21	19838

Antigen processing and presentation of exogenous peptide antigen	BP	3.96	0.02	0.19	30	2478
Positive regulation of phagocytosis	BP	3.96	0.02	0.19	8	50766
Vesicle-mediated transport	BP	3.94	0.02	0.19	112	16192
Coated pit	CC	3.94	0.02	0.19	11	5905
Membrane organization	BP	3.94	0.02	0.19	64	61024
Glycosaminoglycan metabolic process	BP	3.94	0.02	0.19	27	30203
Divalent inorganic cation transmembrane transporter activity	MF	3.94	0.02	0.19	27	72509
Protein localization to membrane	BP	3.93	0.02	0.19	14	72657

Heart looping	BP	3.92	0.02	0.20	12	1947
Cell morphogenesis involved in differentiation	BP	3.92	0.02	0.20	22	904
Anchoring junction	CC	3.90	0.02	0.20	37	70161
Regulation of transcription involved in cell fate commitment	BP	3.89	0.02	0.20	5	60850
Spinal cord association neuron differentiation	BP	3.89	0.02	0.20	5	21527
Intrinsic to internal side of plasma membrane	CC	3.89	0.02	0.20	5	31235
Dorsal/ventral axis specification	BP	3.89	0.02	0.20	5	9950
Regulation of respiratory system process	BP	3.89	0.02	0.20	5	44065
Lens morphogenesis in	BP	3.89	0.02	0.20	5	2089

camera-type eye						
DNA-directed RNA polymerase II, core complex	CC	3.89	0.02	0.20	5	5665
Actin monomer binding	MF	3.89	0.02	0.20	5	3785
Central nervous system neuron development	BP	3.89	0.02	0.20	7	21954
Mesenchymal cell development	BP	3.89	0.02	0.20	7	14031
Positive regulation of glial cell differentiation	BP	3.89	0.02	0.20	7	45687
Zinc ion binding	MF	3.88	0.02	0.20	280	8270
Positive regulation of adenylate cyclase activity	BP	3.86	0.02	0.20	9	45762
Endosomal part	CC	3.86	0.02	0.20	53	44440
Neurotransmitter:sodium	MF	3.85	0.02	0.20	6	5328

symporter activity						
Regulation of transcription regulatory region DNA binding	BP	3.85	0.02	0.20	6	2000677
Cytoskeletal protein binding	MF	3.85	0.02	0.20	97	8092
Regulation of cellular biosynthetic process	BP	3.84	0.02	0.20	458	31326
Regulation of molecular function	BP	3.84	0.02	0.21	254	65009
Anion transmembrane transporter activity	MF	3.83	0.02	0.21	40	8509
Polysaccharide metabolic process	BP	3.83	0.02	0.21	15	5976
Regulation of stem cell differentiation	BP	3.83	0.02	0.21	15	2000736
Anatomical structure	BP	3.82	0.02	0.21	29	60249

homeostasis						
Regulation of interleukin-1 production	BP	3.81	0.02	0.21	10	32652
Stem cell proliferation	BP	3.81	0.02	0.21	10	72089
Antigen processing and presentation of exogenous antigen	BP	3.81	0.02	0.21	30	19884
Myosin complex	CC	3.80	0.02	0.21	14	16459
Membrane part	CC	3.80	0.02	0.21	808	44425
Voltage-gated channel activity	MF	3.80	0.02	0.21	31	22832
Voltage-gated ion channel activity	MF	3.80	0.02	0.21	31	5244
Regulation of adenylate cyclase activity	BP	3.79	0.02	0.21	13	45761
Regulation of cartilage development	BP	3.79	0.02	0.21	11	61035

Positive regulation of lipase activity	BP	3.78	0.02	0.21	17	60193
Organelle membrane	CC	3.78	0.02	0.21	307	31090
Positive regulation of JNK cascade	BP	3.78	0.02	0.21	12	46330
Regulation of cell motility	BP	3.78	0.02	0.21	66	2000145
Synapse	CC	3.78	0.02	0.21	34	45202
Positive regulation of cytoskeleton organization	BP	3.77	0.02	0.21	21	51495
Regulation of neuron projection development	BP	3.77	0.02	0.21	36	10975
Cell part morphogenesis	BP	3.77	0.02	0.21	38	32990
Cell differentiation in spinal cord	BP	3.76	0.02	0.21	8	21515
Face morphogenesis	BP	3.76	0.02	0.21	8	60325

Stem cell development	BP	3.76	0.02	0.21	8	48864
Activation of adenylate cyclase activity	BP	3.76	0.02	0.21	8	7190
Embryo development	BP	3.74	0.02	0.21	52	9790
Heterocyclic compound binding	MF	3.72	0.02	0.22	709	1901363
Regulation of macromolecule metabolic process	BP	3.72	0.02	0.22	565	60255
Stress-activated MAPK cascade	BP	3.72	0.02	0.22	18	51403
Regulation of RNA metabolic process	BP	3.71	0.02	0.22	406	51252
Hexose metabolic process	BP	3.71	0.02	0.22	33	19318
Cell projection organization	BP	3.70	0.02	0.22	75	30030

Positive regulation of chemokine biosynthetic process	BP	3.70	0.02	0.22	4	45080
Hematopoietic stem cell proliferation	BP	3.70	0.02	0.22	4	71425
Regulation of development, heterochronic	BP	3.70	0.02	0.22	4	40034
Apical protein localization	BP	3.70	0.02	0.22	4	45176
Ventricular trabecula myocardium morphogenesis	BP	3.70	0.02	0.22	4	3222
Positive regulation of protein sumoylation	BP	3.70	0.02	0.22	4	33235
Pre-mrna binding	MF	3.70	0.02	0.22	4	36002
Peripheral nervous	BP	3.70	0.02	0.22	4	48935

system neuron development						
Metaphase	BP	3.70	0.02	0.22	4	51323
Regulation of superoxide anion generation	BP	3.70	0.02	0.22	4	32928
Activation of transmembrane receptor protein tyrosine kinase activity	BP	3.70	0.02	0.22	4	7171
DNA synthesis involved in DNA repair	BP	3.70	0.02	0.22	4	731
Positive regulation of SMAD protein import into nucleus	BP	3.70	0.02	0.22	4	60391
Basal transcription machinery binding	MF	3.70	0.02	0.22	4	1098

Basal RNA polymerase II transcription machinery binding	MF	3.70	0.02	0.22	4	1099
Protein domain specific binding	MF	3.69	0.03	0.22	79	19904
Cellular response to endogenous stimulus	BP	3.69	0.03	0.22	100	71495
Heterotrimeric G-protein complex	CC	3.69	0.03	0.22	9	5834
Regulation of lyase activity	BP	3.68	0.03	0.22	14	51339
Amino acid transmembrane transporter activity	MF	3.68	0.03	0.22	14	15171
Voltage-gated cation channel activity	MF	3.68	0.03	0.22	24	22843
Axon part	CC	3.68	0.03	0.22	24	33267

Positive regulation of protein catabolic process	BP	3.68	0.03	0.22	17	45732
Endoderm development	BP	3.67	0.03	0.22	7	7492
Chondroitin sulfate biosynthetic process	BP	3.67	0.03	0.22	7	30206
Dorsal/ventral pattern formation	BP	3.66	0.03	0.22	13	9953
Positive regulation of cell projection organization	BP	3.65	0.03	0.22	25	31346
Recycling endosome	CC	3.64	0.03	0.22	12	55037
Response to organic substance	BP	3.64	0.03	0.22	261	10033
Voltage-gated potassium channel activity	MF	3.63	0.03	0.22	16	5249

Regulation of biosynthetic process	BP	3.63	0.03	0.22	460	9889
Regulation of chemotaxis	BP	3.63	0.03	0.22	20	50920
Response to acid	BP	3.62	0.03	0.22	18	1101
Wnt receptor signaling pathway, calcium modulating pathway	BP	3.62	0.03	0.22	3	7223
Adenylate cyclase binding	MF	3.62	0.03	0.22	3	8179
Regulation of bile acid biosynthetic process	BP	3.62	0.03	0.22	3	70857
Neutrophil degranulation	BP	3.62	0.03	0.22	3	43312
Coumarin metabolic process	BP	3.62	0.03	0.22	3	9804
N-methyl-D-aspartate selective glutamate	MF	3.62	0.03	0.22	3	4972

receptor activity						
FACIT collagen	CC	3.62	0.03	0.22	3	5593
WINAC complex	CC	3.62	0.03	0.22	3	71778
COPI-coated vesicle	CC	3.62	0.03	0.22	3	30137
Eukaryotic initiation factor 4E binding	MF	3.62	0.03	0.22	3	8190
Opioid receptor signaling pathway	BP	3.62	0.03	0.22	3	38003
Nerve growth factor binding	MF	3.62	0.03	0.22	3	48406
Somatic muscle development	BP	3.62	0.03	0.22	3	7525
Positive regulation of non-canonical Wnt receptor signaling pathway	BP	3.62	0.03	0.22	3	2000052
Positive regulation of	BP	3.62	0.03	0.22	3	10890

sequestering of triglyceride						
Coronary vasculature morphogenesis	BP	3.62	0.03	0.22	3	60977
Forebrain anterior/posterior pattern specification	BP	3.62	0.03	0.22	3	21797
Glycine transmembrane transporter activity	MF	3.62	0.03	0.22	3	15187
Laminin-1 binding	MF	3.62	0.03	0.22	3	43237
Growth plate cartilage development	BP	3.62	0.03	0.22	3	3417
Gene silencing by mirna	BP	3.62	0.03	0.22	3	35195
Retina vasculature morphogenesis in camera-type eye	BP	3.62	0.03	0.22	3	61299
Immunoglobulin	BP	3.62	0.03	0.22	3	2377

production						
JUN kinase binding	MF	3.62	0.03	0.22	3	8432
Mitotic metaphase	BP	3.62	0.03	0.22	3	89
Sensory perception of sweet taste	BP	3.62	0.03	0.22	3	50916
Chloride channel regulator activity	MF	3.62	0.03	0.22	3	17081
Collagen biosynthetic process	BP	3.62	0.03	0.22	3	32964
Endothelial cell differentiation	BP	3.60	0.03	0.22	6	45446
Activation of Rho gtpase activity	BP	3.60	0.03	0.22	6	32862
Intracellular ligand-gated ion channel activity	MF	3.60	0.03	0.22	6	5217
Microfilament motor	MF	3.60	0.03	0.22	6	146

activity						
Positive regulation of endocytosis	BP	3.59	0.03	0.22	15	45807
Carbohydrate homeostasis	BP	3.59	0.03	0.22	21	33500
Glucose homeostasis	BP	3.59	0.03	0.22	21	42593
Response to arsenic-containing substance	BP	3.59	0.03	0.22	5	46685
Alpha-mannosidase activity	MF	3.59	0.03	0.22	5	4559
Nua4 histone acetyltransferase complex	CC	3.59	0.03	0.22	5	35267
Axonemal dynein complex	CC	3.59	0.03	0.22	5	5858
Tubulin-tyrosine ligase activity	MF	3.59	0.03	0.22	5	4835

Extracellular region part	CC	3.58	0.03	0.22	160	44421
Negative regulation of cell growth	BP	3.57	0.03	0.22	25	30308
Regulation of lipid biosynthetic process	BP	3.57	0.03	0.22	19	46890
Tissue remodeling	BP	3.56	0.03	0.23	14	48771
Regulation of cell morphogenesis	BP	3.56	0.03	0.23	49	22604
Intracellular membrane-bounded organelle	CC	3.54	0.03	0.23	990	43231
Potassium ion transmembrane transporter activity	MF	3.53	0.03	0.23	23	15079
Metalloendopeptidase activity	MF	3.53	0.03	0.23	20	4222
Negative regulation of cell projection	BP	3.53	0.03	0.23	16	31345

organization						
Regulation of exocytosis	BP	3.53	0.03	0.23	16	17157
Endocytic vesicle	CC	3.53	0.03	0.23	16	30139
Stress-activated protein kinase signaling cascade	BP	3.52	0.03	0.23	18	31098
Adenyl ribonucleotide binding	MF	3.52	0.03	0.23	212	32559
Cellular response to amino acid stimulus	BP	3.52	0.03	0.23	9	71230
In utero embryonic development	BP	3.51	0.03	0.23	35	1701
Phosphotransferase activity, alcohol group as acceptor	MF	3.51	0.03	0.23	107	16773
Intracellular organelle lumen	CC	3.51	0.03	0.23	80	70013

Neurotrophin TRK receptor signaling pathway	BP	3.51	0.03	0.23	44	48011
Embryonic organ development	BP	3.50	0.03	0.23	21	48568
Regulation of lipase activity	BP	3.50	0.03	0.23	21	60191
Skin development	BP	3.50	0.03	0.23	10	43588
Amide biosynthetic process	BP	3.50	0.03	0.23	11	43604
Protein kinase activity	MF	3.48	0.03	0.24	91	4672
Regulation of cell-cell adhesion	BP	3.48	0.03	0.24	15	22407
Epithelial cell differentiation	BP	3.48	0.03	0.24	41	30855
Embryonic limb morphogenesis	BP	3.47	0.03	0.24	17	30326

Embryonic appendage morphogenesis	BP	3.47	0.03	0.24	17	35113
ATP binding	MF	3.47	0.03	0.24	208	5524
Negative regulation of intracellular steroid hormone receptor signaling pathway	BP	3.46	0.03	0.24	7	33144
Vesicle docking involved in exocytosis	BP	3.46	0.03	0.24	7	6904
Glutamate receptor activity	MF	3.46	0.03	0.24	7	8066
Ephrin receptor signaling pathway	BP	3.46	0.03	0.24	7	48013
Negative regulation of stress-activated MAPK cascade	BP	3.46	0.03	0.24	7	32873
Negative regulation of	BP	3.46	0.03	0.24	7	70303

stress-activated protein kinase signaling cascade						
Neurotrophin signaling pathway	BP	3.45	0.03	0.24	44	38179
Transporter activity	MF	3.43	0.03	0.24	170	5215
Monosaccharide catabolic process	BP	3.42	0.03	0.25	16	46365
Notch signaling pathway	BP	3.41	0.03	0.25	21	7219
Positive regulation of stress-activated MAPK cascade	BP	3.41	0.03	0.25	13	32874
Positive regulation of cell-substrate adhesion	BP	3.41	0.03	0.25	13	10811
Organelle localization	BP	3.41	0.03	0.25	13	51640
Lysosomal membrane	CC	3.41	0.03	0.25	26	5765
Adenyl nucleotide	MF	3.40	0.03	0.25	212	30554

binding						
Proteinaceous extracellular matrix	CC	3.39	0.03	0.25	36	5578
Calcium ion transmembrane transporter activity	MF	3.39	0.03	0.25	22	15085
Chordate embryonic development	BP	3.39	0.03	0.25	35	43009
Endoplasmic reticulum lumen	CC	3.39	0.03	0.25	29	5788
Regulation of Ras gtpase activity	BP	3.39	0.03	0.25	29	32318
Antigen processing and presentation of peptide antigen	BP	3.38	0.03	0.25	31	48002
Response to amino acid stimulus	BP	3.37	0.03	0.25	15	43200

Positive regulation of phospholipase activity	BP	3.37	0.03	0.25	15	10518
Transition metal ion binding	MF	3.37	0.03	0.25	308	46914
Negative regulation of response to external stimulus	BP	3.37	0.03	0.25	23	32102
Regulation of gene expression	BP	3.37	0.03	0.25	455	10468
Regulation of embryonic development	BP	3.37	0.03	0.25	17	45995
Macromolecule metabolic process	BP	3.37	0.03	0.25	834	43170
Cellular macromolecule biosynthetic process	BP	3.37	0.03	0.25	355	34645
Polysaccharide catabolic process	BP	3.37	0.03	0.25	6	272

Adipose tissue development	BP	3.37	0.03	0.25	6	60612
Cardiac cell development	BP	3.37	0.03	0.25	6	55006
Homeostasis of number of cells within a tissue	BP	3.37	0.03	0.25	6	48873
Negative regulation of protein kinase B signaling cascade	BP	3.37	0.03	0.25	6	51898
Regulation of interleukin-4 production	BP	3.37	0.03	0.25	6	32673
Regulation of RNA biosynthetic process	BP	3.36	0.03	0.25	395	2001141
Negative regulation of muscle cell differentiation	BP	3.36	0.03	0.25	9	51148
Negative regulation of	BP	3.36	0.03	0.25	9	1901185

ERBB signaling pathway						
Negative regulation of epidermal growth factor receptor signaling pathway	BP	3.36	0.03	0.25	9	42059
Positive regulation of proteasomal protein catabolic process	BP	3.36	0.03	0.25	9	1901800
Integral to plasma membrane	CC	3.35	0.04	0.25	145	5887
MHC protein complex	CC	3.35	0.04	0.25	10	42611
RNA polymerase activity	MF	3.35	0.04	0.25	10	34062
DNA-directed RNA polymerase activity	MF	3.35	0.04	0.25	10	3899
Regulation of organ morphogenesis	BP	3.34	0.04	0.25	25	2000027

Glandular epithelial cell development	BP	3.34	0.04	0.25	4	2068
Negative chemotaxis	BP	3.34	0.04	0.25	4	50919
Intramolecular transferase activity, phosphotransferases	MF	3.34	0.04	0.25	4	16868
Positive regulation of translational initiation	BP	3.34	0.04	0.25	4	45948
Platelet alpha granule	CC	3.34	0.04	0.25	4	31091
Heart trabecula morphogenesis	BP	3.34	0.04	0.25	4	61384
Myelin maintenance	BP	3.34	0.04	0.25	4	43217
Regulation of Wnt receptor signaling pathway, planar cell polarity pathway	BP	3.34	0.04	0.25	4	2000095
Regulation of antigen	BP	3.34	0.04	0.25	4	2577

processing and presentation						
Dipeptidyl-peptidase activity	MF	3.34	0.04	0.25	4	8239
Positive regulation of steroid biosynthetic process	BP	3.34	0.04	0.25	4	10893
RNA polymerase core enzyme binding	MF	3.34	0.04	0.25	4	43175
Phosphorylation	BP	3.34	0.04	0.25	96	16310
Positive regulation of organ growth	BP	3.32	0.04	0.25	5	46622
Translation initiation factor binding	MF	3.32	0.04	0.25	5	31369
Nitric oxide mediated signal transduction	BP	3.32	0.04	0.25	5	7263
Organ formation	BP	3.32	0.04	0.25	5	48645

Vitamin D receptor binding	MF	3.32	0.04	0.25	5	42809
H4/H2A histone acetyltransferase complex	CC	3.32	0.04	0.25	5	43189
Negative regulation of toll-like receptor signaling pathway	BP	3.32	0.04	0.25	5	34122
Nucleotide-sugar biosynthetic process	BP	3.32	0.04	0.25	5	9226
Regulation of cellular macromolecule biosynthetic process	BP	3.31	0.04	0.25	426	2000112
Calcium ion binding	MF	3.29	0.04	0.25	99	5509
Positive regulation of stress-activated protein kinase signaling	BP	3.29	0.04	0.25	13	70304

cascade						
Positive regulation of phospholipase C activity	BP	3.29	0.04	0.25	13	10863
Monosaccharide metabolic process	BP	3.27	0.04	0.25	36	5996
Basement membrane	CC	3.27	0.04	0.25	15	5604
Hexose catabolic process	BP	3.27	0.04	0.25	15	19320
Positive regulation of neural precursor cell proliferation	BP	3.27	0.04	0.25	7	2000179
Substrate adhesion-dependent cell spreading	BP	3.27	0.04	0.25	7	34446
Calcium-dependent cell-cell adhesion	BP	3.27	0.04	0.25	7	16339
Enhancer sequence-	MF	3.27	0.04	0.25	7	1158

specific DNA binding						
Regulated secretory pathway	BP	3.27	0.04	0.25	7	45055
Autophagic vacuole	CC	3.27	0.04	0.25	7	5776
Positive regulation of stem cell proliferation	BP	3.26	0.04	0.25	12	2000648
Activation of phospholipase C activity	BP	3.26	0.04	0.25	12	7202
Chondroitin sulfate metabolic process	BP	3.26	0.04	0.25	12	30204
Calmodulin binding	MF	3.25	0.04	0.25	28	5516
Positive regulation of interleukin-6 production	BP	3.22	0.04	0.25	8	32755
Regulation of actin filament depolymerization	BP	3.22	0.04	0.25	8	30834
Negative regulation of	BP	3.22	0.04	0.25	8	10812

cell-substrate adhesion						
Cell projection morphogenesis	BP	3.21	0.04	0.25	35	48858
Actin cytoskeleton reorganization	BP	3.20	0.04	0.25	9	31532
Extracellular matrix binding	MF	3.20	0.04	0.25	9	50840
Ammonium transmembrane transport	BP	3.20	0.04	0.25	2	72488
Prostaglandin-E synthase activity	MF	3.20	0.04	0.25	2	50220
Trehalose metabolic process	BP	3.20	0.04	0.25	2	5991
Seminiferous tubule development	BP	3.20	0.04	0.25	2	72520
Cardiac atrium	BP	3.20	0.04	0.25	2	3209

morphogenesis						
Regulation of collateral sprouting in absence of injury	BP	3.20	0.04	0.25	2	48696
Spemann organizer formation	BP	3.20	0.04	0.25	2	60061
Regulation of exocyst localization	BP	3.20	0.04	0.25	2	60178
Dehydroascorbic acid transporter activity	MF	3.20	0.04	0.25	2	33300
D-glucose transmembrane transporter activity	MF	3.20	0.04	0.25	2	55056
Production of mirnas involved in gene silencing by mirna	BP	3.20	0.04	0.25	2	35196
Melatonin receptor	MF	3.20	0.04	0.25	2	8502

activity						
Hypothalamus cell differentiation	BP	3.20	0.04	0.25	2	21979
Collagen type IX	CC	3.20	0.04	0.25	2	5594
Negative regulation of transcription by transcription factor localization	BP	3.20	0.04	0.25	2	10621
Detection of endogenous stimulus	BP	3.20	0.04	0.25	2	9726
Autonomic nervous system development	BP	3.20	0.04	0.25	2	48483
Trophectodermal cellular morphogenesis	BP	3.20	0.04	0.25	2	1831
Sec61 translocon complex	CC	3.20	0.04	0.25	2	5784
Translocon complex	CC	3.20	0.04	0.25	2	71256

Brain segmentation	BP	3.20	0.04	0.25	2	35284
Cell migration involved in endocardial cushion formation	BP	3.20	0.04	0.25	2	3273
Transcription initiation from RNA polymerase III promoter	BP	3.20	0.04	0.25	2	6384
Calcium ion-dependent exocytosis of neurotransmitter	BP	3.20	0.04	0.25	2	48791
Dendritic growth cone	CC	3.20	0.04	0.25	2	44294
Natriuretic peptide receptor activity	MF	3.20	0.04	0.25	2	16941
Metencephalon development	BP	3.20	0.04	0.25	2	22037
Diencephalon morphogenesis	BP	3.20	0.04	0.25	2	48852

Cardiac vascular smooth muscle cell development	BP	3.20	0.04	0.25	2	60948
Vasoactive intestinal polypeptide receptor activity	MF	3.20	0.04	0.25	2	4999
Transcription initiation from mitochondrial promoter	BP	3.20	0.04	0.25	2	6391
G-quadruplex DNA binding	MF	3.20	0.04	0.25	2	51880
Butyrate metabolic process	BP	3.20	0.04	0.25	2	19605
Chromosome movement towards spindle pole	BP	3.20	0.04	0.25	2	51305
Phenylpropanoid catabolic process	BP	3.20	0.04	0.25	2	46271

Cerebral cortex regionalization	BP	3.20	0.04	0.25	2	21796
Regulation of defense response to bacterium	BP	3.20	0.04	0.25	2	1900424
Regulation of phagocytosis, engulfment	BP	3.20	0.04	0.25	2	60099
Positive regulation of phagocytosis, engulfment	BP	3.20	0.04	0.25	2	60100
Cellular pigmentation	BP	3.20	0.04	0.25	2	33059
Synaptic cleft	CC	3.20	0.04	0.25	2	43083
Regulation of nodal signaling pathway involved in determination of left/right asymmetry	BP	3.20	0.04	0.25	2	1900145

Regulation of nodal signaling pathway involved in determination of lateral mesoderm left/right asymmetry	BP	3.20	0.04	0.25	2	1900175
Establishment or maintenance of neuroblast polarity	BP	3.20	0.04	0.25	2	45196
Establishment of neuroblast polarity	BP	3.20	0.04	0.25	2	45200
Sensory system development	BP	3.20	0.04	0.25	2	48880
Cardiac muscle cell myoblast differentiation	BP	3.20	0.04	0.25	2	60379
Collagen V binding	MF	3.20	0.04	0.25	2	70052
Forebrain neuron fate	BP	3.20	0.04	0.25	2	21877

commitment						
Regulation of transcription from RNA polymerase II promoter involved in spinal cord motor neuron fate specification	BP	3.20	0.04	0.25	2	21912
Neural plate pattern specification	BP	3.20	0.04	0.25	2	60896
Neural plate regionalization	BP	3.20	0.04	0.25	2	60897
Synaptic vesicle clustering	BP	3.20	0.04	0.25	2	97091
Bombesin receptor activity	MF	3.20	0.04	0.25	2	4946
Locomotion involved in locomotory behavior	BP	3.20	0.04	0.25	2	31987

Regulation of transcription from RNA polymerase II promoter involved in determination of left/right symmetry	BP	3.20	0.04	0.25	2	1900094
Nodal signaling pathway involved in determination of lateral mesoderm left/right asymmetry	BP	3.20	0.04	0.25	2	1900164
Nodal signaling pathway involved in determination of left/right asymmetry	BP	3.20	0.04	0.25	2	38107
Smooth muscle cell proliferation	BP	3.20	0.04	0.25	2	48659

Pre-mrna intronic binding	MF	3.20	0.04	0.25	2	97157
Intestinal epithelial cell development	BP	3.20	0.04	0.25	2	60576
Negative regulation of cholesterol biosynthetic process	BP	3.20	0.04	0.25	2	45541
Negative regulation of cholesterol metabolic process	BP	3.20	0.04	0.25	2	90206
Actin polymerization-dependent cell motility	BP	3.20	0.04	0.25	2	70358
Protein poly-ADP-ribosylation	BP	3.20	0.04	0.25	2	70212
Viral assembly, maturation, egress, and release	BP	3.20	0.04	0.25	2	19067

Retinal blood vessel morphogenesis	BP	3.20	0.04	0.25	2	61304
Ornithine decarboxylase activator activity	MF	3.20	0.04	0.25	2	42978
Intestine smooth muscle contraction	BP	3.20	0.04	0.25	2	14827
Calcium-dependent protein kinase C activity	MF	3.20	0.04	0.25	2	4698
Calcium-dependent protein serine/threonine kinase activity	MF	3.20	0.04	0.25	2	9931
Laminin-11 complex	CC	3.20	0.04	0.25	2	43260
Positive regulation of hydrolase activity	BP	3.19	0.04	0.25	69	51345
Regulation of MAPK cascade	BP	3.19	0.04	0.25	71	43408
Ubiquitin protein ligase	MF	3.19	0.04	0.25	26	31625

binding						
Small conjugating protein ligase binding	MF	3.19	0.04	0.25	26	44389
Transcription initiation from RNA polymerase II promoter	BP	3.19	0.04	0.25	31	6367
Regulation of purine nucleotide biosynthetic process	BP	3.18	0.04	0.25	20	1900371
Regulation of nucleotide biosynthetic process	BP	3.18	0.04	0.25	20	30808
Transcriptional repressor complex	CC	3.18	0.04	0.25	13	17053
Ion transport	BP	3.17	0.04	0.25	130	6811
Regulation of transcription, DNA-dependent	BP	3.17	0.04	0.25	391	6355

Positive regulation of purine nucleotide metabolic process	BP	3.17	0.04	0.25	15	1900544
Negative regulation of binding	BP	3.17	0.04	0.25	15	51100
Wnt receptor signaling pathway, planar cell polarity pathway	BP	3.16	0.04	0.25	6	60071
Regulation of establishment of planar polarity	BP	3.16	0.04	0.25	6	90175
Negative regulation of glial cell differentiation	BP	3.16	0.04	0.25	6	45686
Motor neuron axon guidance	BP	3.16	0.04	0.25	6	8045
Laminin binding	MF	3.16	0.04	0.25	6	43236
Regulation of cytokine	BP	3.15	0.04	0.25	3	2739

secretion involved in immune response						
Galactose catabolic process	BP	3.15	0.04	0.25	3	19388
Filtration diaphragm	CC	3.15	0.04	0.25	3	36056
Slit diaphragm	CC	3.15	0.04	0.25	3	36057
Relaxation of smooth muscle	BP	3.15	0.04	0.25	3	44557
Embryonic process involved in female pregnancy	BP	3.15	0.04	0.25	3	60136
Regulation of neuron migration	BP	3.15	0.04	0.25	3	2001222
Cellular extravasation	BP	3.15	0.04	0.25	3	45123
Interkinetic nuclear migration	BP	3.15	0.04	0.25	3	22027
CD4-positive or CD8-	BP	3.15	0.04	0.25	3	43369

positive, alpha-beta T cell lineage commitment						
H3 histone acetyltransferase complex	CC	3.15	0.04	0.25	3	70775
MOZ/MORF histone acetyltransferase complex	CC	3.15	0.04	0.25	3	70776
Trna transcription	BP	3.15	0.04	0.25	3	9304
Neuronal cell body membrane	CC	3.15	0.04	0.25	3	32809
Cell body membrane	CC	3.15	0.04	0.25	3	44298
MAP-kinase scaffold activity	MF	3.15	0.04	0.25	3	5078
Positive regulation of dendritic cell antigen processing and	BP	3.15	0.04	0.25	3	2606

presentation						
Nuclear envelope lumen	CC	3.15	0.04	0.25	3	5641
Laminin-1 complex	CC	3.15	0.04	0.25	3	5606
Cell cortex part	CC	3.15	0.04	0.25	18	44448
Enzyme activator activity	MF	3.15	0.04	0.25	64	8047
Protein secretion	BP	3.14	0.04	0.26	12	9306
Regulation of cell migration	BP	3.13	0.04	0.26	61	30334
Regulation of neurotransmitter levels	BP	3.12	0.04	0.26	16	1505
Visual perception	BP	3.12	0.04	0.26	30	7601
Dendrite	CC	3.12	0.04	0.26	30	30425
Detection of external stimulus	BP	3.12	0.04	0.26	26	9581
Monocarboxylic acid biosynthetic process	BP	3.12	0.04	0.26	28	72330

Central nervous system development	BP	3.10	0.04	0.26	20	7417
Activating transcription factor binding	MF	3.10	0.04	0.26	11	33613
Negative regulation of cellular response to growth factor stimulus	BP	3.09	0.05	0.27	17	90288
G-protein coupled peptide receptor activity	MF	3.09	0.05	0.27	21	8528
E-box binding	MF	3.08	0.05	0.27	7	70888
Myeloid cell activation involved in immune response	BP	3.08	0.05	0.27	7	2275
Vesicle docking	BP	3.08	0.05	0.27	7	48278
Excretion	BP	3.07	0.05	0.27	10	7588
Negative regulation of steroid biosynthetic	BP	3.07	0.05	0.27	5	10894

process						
SMAD protein signal transduction	BP	3.07	0.05	0.27	5	60395
External encapsulating structure part	CC	3.07	0.05	0.27	5	44462
RNA polymerase II distal enhancer sequence-specific DNA binding	MF	3.07	0.05	0.27	5	980
Mannosidase activity	MF	3.07	0.05	0.27	5	15923
Positive regulation of neuroblast proliferation	BP	3.07	0.05	0.27	5	2052
Protein phosphatase 2A binding	MF	3.07	0.05	0.27	5	51721
Histone acetyltransferase binding	MF	3.07	0.05	0.27	5	35035

Regulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate selective glutamate receptor activity	BP	3.07	0.05	0.27	5	2000311
Protein targeting to plasma membrane	BP	3.07	0.05	0.27	5	72661
Muscle cell proliferation	BP	3.07	0.05	0.27	5	33002
Positive regulation of nucleotide metabolic process	BP	3.07	0.05	0.27	15	45981
Cellular polysaccharide metabolic process	BP	3.07	0.05	0.27	13	44264
Potassium ion transport	BP	3.06	0.05	0.27	18	6813
Lateral plasma membrane	CC	3.06	0.05	0.27	8	16328

Defense response to Gram-positive bacterium	BP	3.06	0.05	0.27	8	50830
Positive regulation of exocytosis	BP	3.06	0.05	0.27	8	45921
Receptor regulator activity	MF	3.06	0.05	0.27	9	30545
Cardiocyte differentiation	BP	3.06	0.05	0.27	9	35051
Forelimb morphogenesis	BP	3.06	0.05	0.27	9	35136
Positive regulation of axonogenesis	BP	3.06	0.05	0.27	9	50772
Phagocytosis	BP	3.06	0.05	0.27	9	6909
Cell-cell adhesion	BP	3.06	0.05	0.27	54	16337
Transcription regulatory region sequence-specific DNA binding	MF	3.05	0.05	0.27	28	976

Regulation of macromolecule biosynthetic process	BP	3.05	0.05	0.27	434	10556
Chemical homeostasis	BP	3.04	0.05	0.27	107	48878
Oxidation-reduction process	BP	3.04	0.05	0.27	73	55114
Leydig cell differentiation	BP	3.04	0.05	0.27	4	33327
Trabecula morphogenesis	BP	3.04	0.05	0.27	4	61383
Positive regulation of interferon-gamma biosynthetic process	BP	3.04	0.05	0.27	4	45078
Positive regulation of insulin-like growth factor receptor signaling pathway	BP	3.04	0.05	0.27	4	43568

Mitogen-activated protein kinase kinase binding	MF	3.04	0.05	0.27	4	31434
Regulation of non-canonical Wnt receptor signaling pathway	BP	3.04	0.05	0.27	4	2000050
Chronic inflammatory response	BP	3.04	0.05	0.27	4	2544
Regulation of SMAD protein import into nucleus	BP	3.04	0.05	0.27	4	60390
Regulation of steroid hormone biosynthetic process	BP	3.04	0.05	0.27	4	90030
Histone H2A acetylation	BP	3.04	0.05	0.27	4	43968
Negative regulation of JUN kinase activity	BP	3.04	0.05	0.27	4	43508

Fibrillar collagen	CC	3.04	0.05	0.27	4	5583
Cellular response to chemical stimulus	BP	3.03	0.05	0.27	214	70887
Regulation of phospholipase activity	BP	3.03	0.05	0.27	16	10517
Positive regulation of locomotion	BP	3.02	0.05	0.27	39	40017
Fatty acid biosynthetic process	BP	3.02	0.05	0.27	20	6633
Telomere maintenance	BP	3.02	0.05	0.27	12	723
Steroid metabolic process	BP	3.01	0.05	0.27	38	8202
Golgi cisterna membrane	CC	3.01	0.05	0.27	14	32580
Peptide receptor activity	MF	3.01	0.05	0.27	21	1653
Epidermal growth factor receptor signaling	BP	3.00	0.05	0.27	31	7173

pathway						
Regulation of cytokine biosynthetic process	BP	3.00	0.05	0.27	17	42035
Positive regulation of MAPK cascade	BP	3.00	0.05	0.27	30	43410
Cellular chemical homeostasis	BP	3.00	0.05	0.27	80	55082
Nervous system development	BP	2.99	0.05	0.27	44	7399
Endopeptidase inhibitor activity	MF	2.99	0.05	0.28	28	4866
Endoplasmic reticulum-Golgi intermediate compartment	CC	2.98	0.05	0.28	11	5793
Extrinsic to internal side of plasma membrane	CC	2.98	0.05	0.28	11	31234
Regulation of striated	BP	2.97	0.05	0.28	15	51153

muscle cell differentiation						
Regulation of interferon-gamma production	BP	2.96	0.05	0.28	13	32649
Positive regulation of interleukin-1 beta production	BP	2.96	0.05	0.28	6	32731
Calcium activated cation channel activity	MF	2.96	0.05	0.28	6	5227
Regulation of oligodendrocyte differentiation	BP	2.96	0.05	0.28	6	48713
Neural tube development	BP	2.96	0.05	0.28	6	21915
Phosphatidylinositol 3-kinase binding	MF	2.96	0.05	0.28	6	43548
Middle ear	BP	2.96	0.05	0.28	6	42474

morphogenesis						
Positive regulation of cellular component biogenesis	BP	2.96	0.05	0.28	6	44089
Cellular homeostasis	BP	2.95	0.05	0.28	91	19725
ERBB signaling pathway	BP	2.94	0.05	0.28	31	38127
Cellular macromolecule localization	BP	2.94	0.05	0.29	36	70727
Regulation of ERK1 and ERK2 cascade	BP	2.93	0.05	0.29	21	70372
Regulation of hydrolase activity	BP	2.93	0.05	0.29	110	51336
Regulation of intracellular protein kinase cascade	BP	2.93	0.05	0.29	101	10627
Protein binding, bridging	MF	2.93	0.05	0.29	22	30674

Response to oxygen-containing compound	BP	2.92	0.05	0.29	135	1901700
Ventricular cardiac muscle tissue morphogenesis	BP	2.92	0.05	0.29	9	55010
Neuron-neuron synaptic transmission	BP	2.92	0.05	0.29	9	7270
Hindlimb morphogenesis	BP	2.92	0.05	0.29	9	35137
Regulation of cellular response to growth factor stimulus	BP	2.92	0.05	0.29	26	90287
Homophilic cell adhesion	BP	2.92	0.05	0.29	24	7156
Cellular response to organic substance	BP	2.92	0.05	0.29	184	71310
Protein tyrosine kinase	MF	2.92	0.05	0.29	25	4713

activity						
Locomotory behavior	BP	2.92	0.05	0.29	25	7626
Receptor activator activity	MF	2.91	0.05	0.29	7	30546
Negative regulation of gliogenesis	BP	2.91	0.05	0.29	7	14014
Golgi-associated vesicle	CC	2.91	0.05	0.29	7	5798
Positive regulation of proteolysis	BP	2.91	0.05	0.29	14	45862
Extracellular ligand-gated ion channel activity	MF	2.91	0.05	0.29	14	5230
Telomere organization	BP	2.91	0.05	0.29	12	32200
Negative regulation of BMP signaling pathway	BP	2.91	0.05	0.29	8	30514
Frizzled binding	MF	2.91	0.05	0.29	8	5109
Delayed rectifier	MF	2.91	0.05	0.29	8	5251

	potassium channel
	activity

627 BP, Biological process; MF, molecular function; cellular component; #, number of; GO ID, gene ontology identification.

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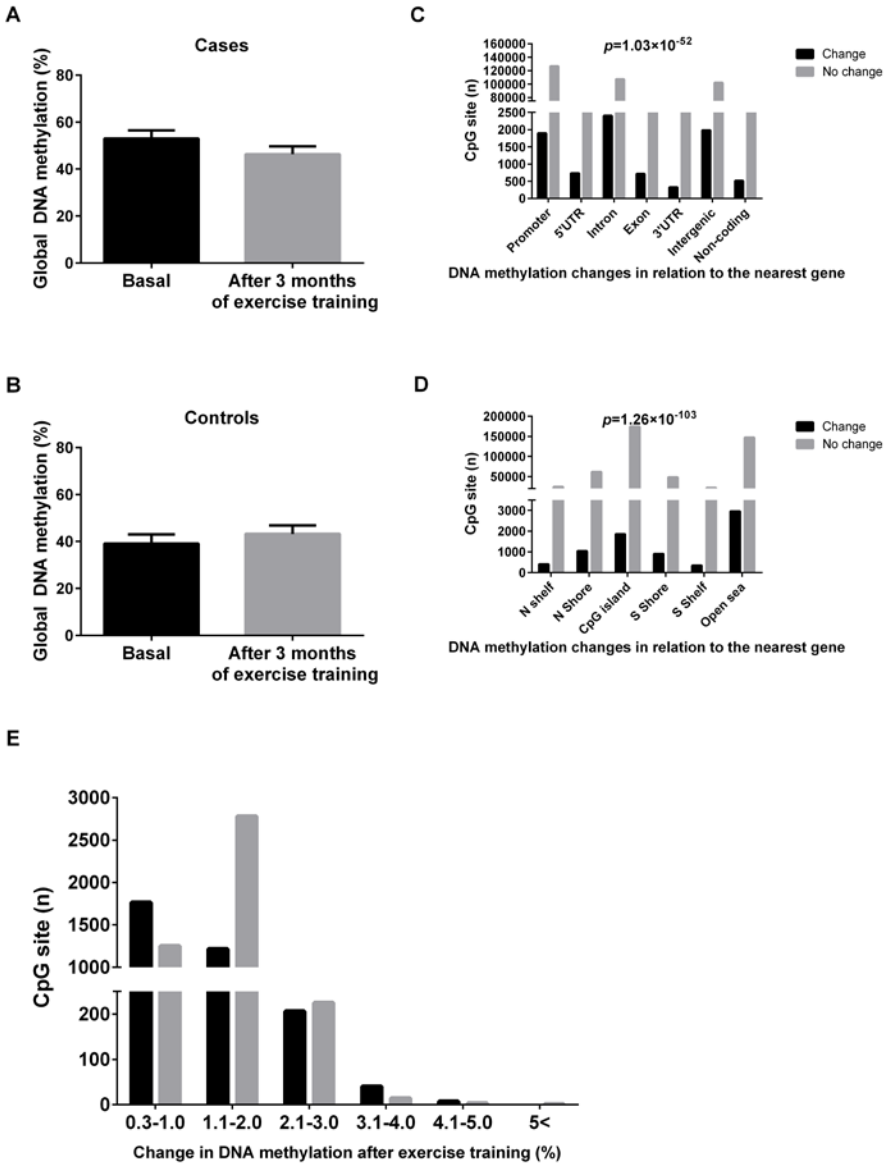
A
Cases
Global DNA methylation (%)
Basal
After 3 months of exercise training
B
Controls
Global DNA methylation (%)
Basal
After 3 months of exercise training
C
p=1.03×10-52
Change
No change
CpG site (n)
Promoter
5'UTR
Intron
Exon
3'UTR
Intergenic
Non-coding
DNA methylation changes in relation to the nearest gene
D
p=1.26×10-103
Change
No change
CpG site (n)
N shelf
N Shore
CpG island
S Shore
S Shelf
Open sea
DNA methylation changes in relation to the nearest gene
E
CpG site (n)
0.3-1.0
1.1-2.0
2.1-3.0
3.1-4.0
4.1-5.0
5<
Change in DNA methylation after exercise training (%)

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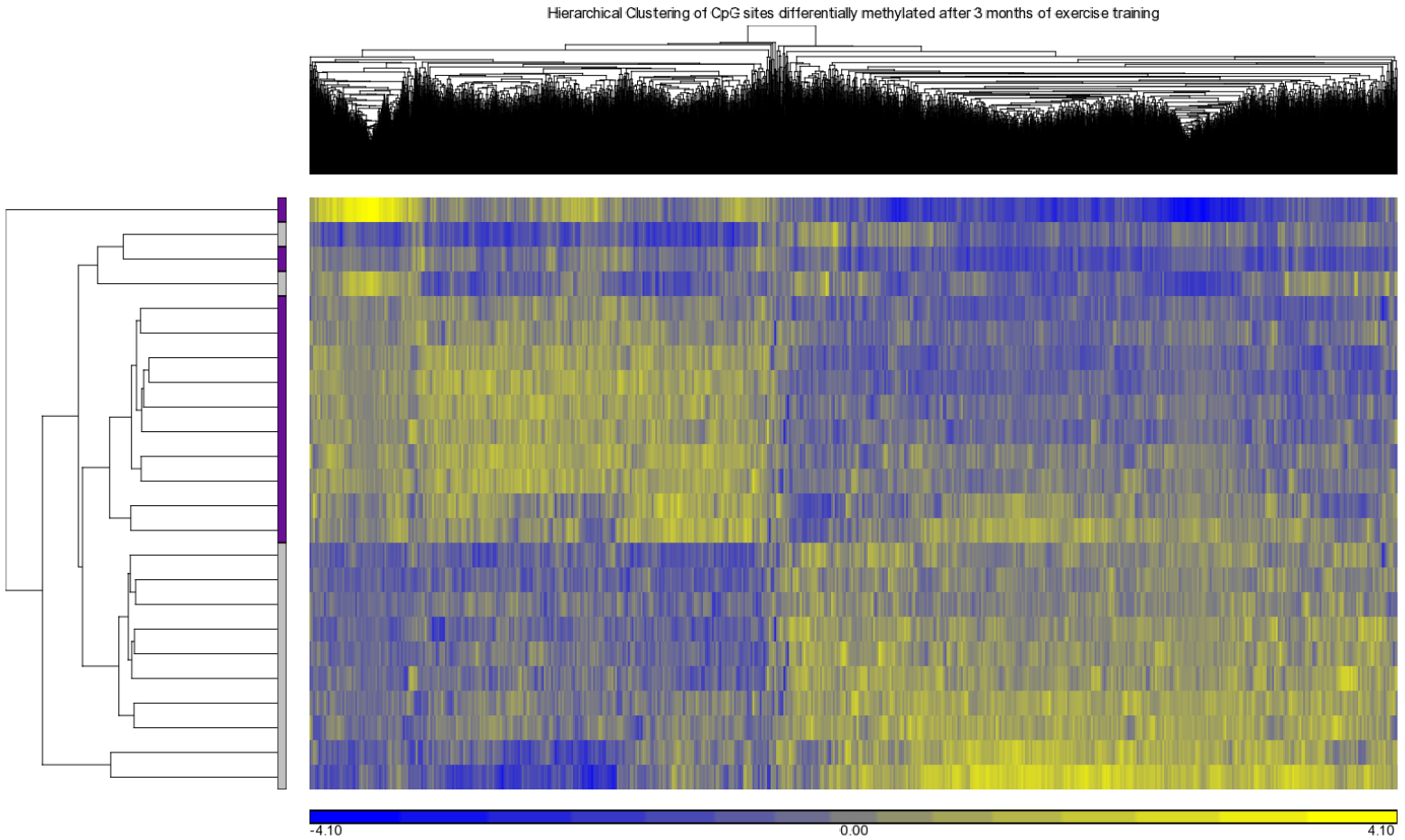

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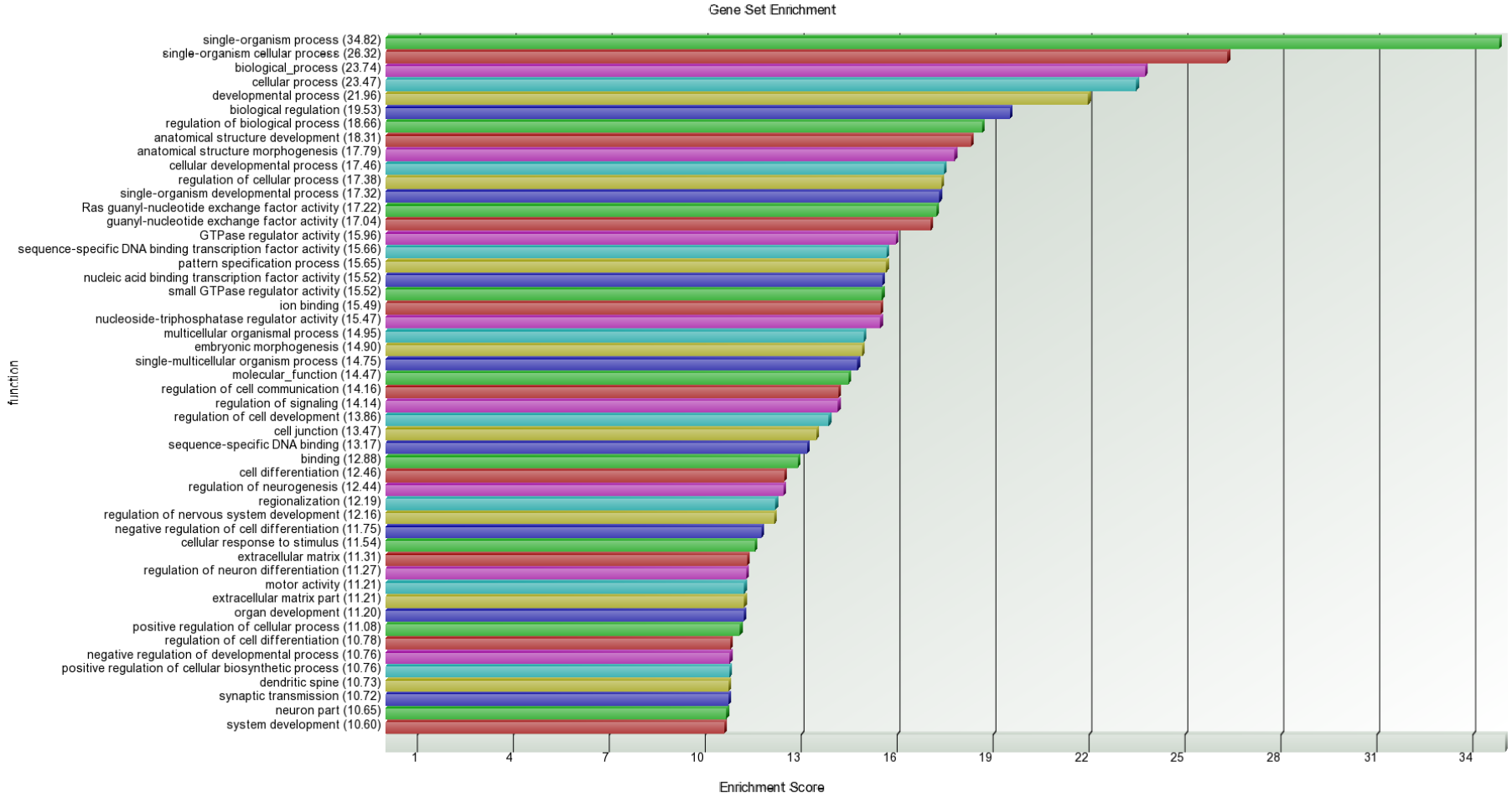
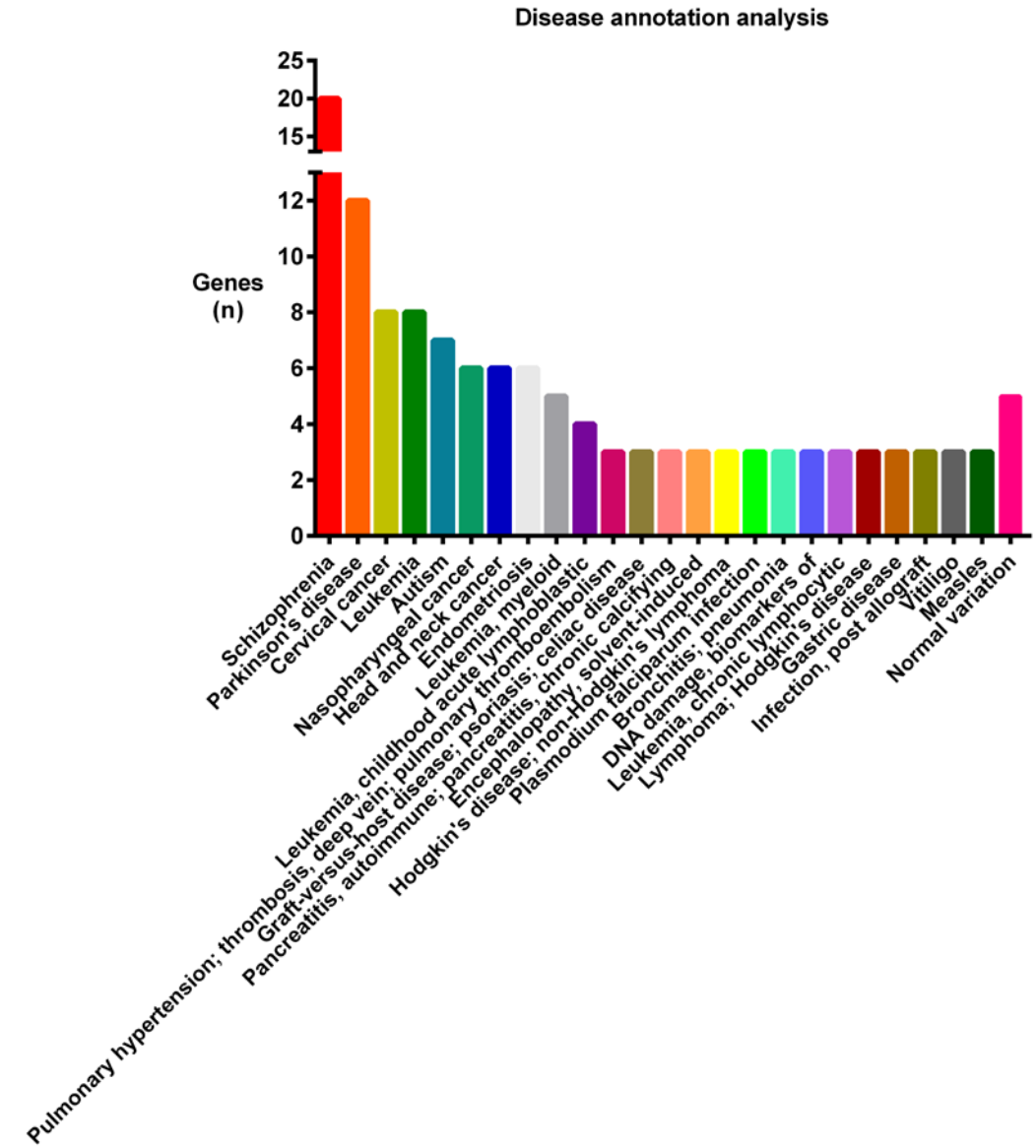

Gene Set Enrichment
single-organism process (34.82)
single-organism cellular process (26.32)
biological_process (23.74)
cellular process (23.47)
developmental process (21.96)
biological regulation (19.53)
regulation of biological process (18.66)
anatomical structure development (18.31)
anatomical structure morphogenesis (17.79)
cellular developmental process (17.46)
regulation of cellular process (17.38)
single-organism developmental process (17.32)
Ras guanyl-nucleotide exchange factor activity (17.22)
guanyl-nucleotide exchange factor activity (17.04)
GTPase regulator activity (15.96)
sequence-specific DNA binding transcription factor activity (15.66)
pattern specification process (15.65)
nucleic acid binding transcription factor activity (15.52)
small GTPase regulator activity (15.52)
ion binding (15.49)
nucleoside-triphosphatase regulator activity (15.47)
multicellular organismal process (14.95)
embryonic morphogenesis (14.90)
single-multicellular organism process (14.75)
molecular_function (14.47)
regulation of cell communication (14.16)
regulation of signaling (14.14)
regulation of cell development (13.86)
cell junction (13.47)
sequence-specific DNA binding (13.17)
binding (12.88)
cell differentiation (12.46)
regulation of neurogenesis (12.44)
regionalization (12.19)
regulation of nervous system development (12.16)
negative regulation of cell differentiation (11.75)
cellular response to stimulus (11.54)
extracellular matrix (11.31)
regulation of neuron differentiation (11.27)
motor activity (11.21)
extracellular matrix part (11.21)
organ development (11.20)
positive regulation of cellular process (11.08)
regulation of cell differentiation (10.78)
negative regulation of developmental process (10.76)
positive regulation of cellular biosynthetic process (10.76)
dendritic spine (10.73)
synaptic transmission (10.72)
neuron part (10.65)
system development (10.60)
function
1
4
7
10
13
16
19
22
25
28
31
34
Enrichment Score


Disease annotation analysis
Genes (n)
25
20
15
12
10
8
6
4
2
0
Schizophrenia
Parkinson's disease
Cervical cancer
Leukemia
Autism
Nasopharyngeal cancer
Head and neck cancer
Endometriosis
Leukemia, myeloid
Leukemia, childhood acute lymphoblastic
Pulmonary hypertension; thrombosis, deep vein; pulmonary thromboembolism
Graft-versus-host disease; psoriasis; celiac disease
Pancreatitis, autoimmune; pancreatitis, chronic calcifying
Encephalopathy, solvent-induced
Hodgkin's disease; non-Hodgkin's lymphoma
Plasmodium falciparum infection
Bronchitis; pneumonia
DNA damage, biomarkers of
Leukemia, chronic lymphocytic
Lymphoma; Hodgkin's disease
Gastric disease
Infection, post allograft
Vitiligo
Measles
Normal variation

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